University of Alberta

Compensatory Corrective Responses Induced by Cutaneous Nerve Stimulation in the Hand and Foot During Walking

by

Carlos Haridas

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

Faculty of Physical Education and Recreation

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Abstract

The present study investigated interlimb cutaneous reflexes during walking. Subjects walked on a treadmill while reflexes were elicited by electrical stimulation delivered to cutaneous nerves, one at the foot and one in the wrist. EMG and kinematic data were collected bilaterally from muscles of the lower and upper extremities. Phase-modulated interlimb reflexes were observed at the middle latency period (80-120 ms) for the muscles of the lower extremities, as well as for posterior deltoid. Additionally, during the stance-swing transition for each ankle, an increase in plantar flexion was seen in the ipsilateral ankle with superficial peroneal (SP) stimulation, while dorsiflexion was seen in the contralateral ankle. At the same position of the step cycle during superficial radial (SR) stimulation, both ankles showed an increased dorsiflexion. The results suggest that interlimb reflexes are gated by a central pattern generator, and serve to assist in a stumble-corrective / stumble-avoidance response during walking.

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CHAPTER 1 - Introduction

Coordination between the forelimbs and hindlimbs in cats is a crucial task that must be accomplished in order to allow for the smooth progression of locomotion and to maintain balance (Duysens & Tax, 1994). Interlimb reflexes are thought to assist in this task, by supporting limb coordination and movements when encountering a perturbation during locomotion (Forssberg et al., 1975; Miller et al., 1975). There is partial evidence that this coordination in the cat is preserved in the human, existing between the arms and legs (Dietz et al., 2001; Wannier et al., 2001). Interlimb reflexes were shown to exist in humans by Zehr et al. (2001a), however these reflexes were evoked during static conditions. The authors suggested that a propriospinal pathway could mediate part of the interlimb reflexes observed, and that this may be used to coordinate movement between the arms and legs during walking. The existence of these reflexes suggests that there may be a similar control mechanism across species for coordination between the limbs during movement. However, these reflexes have not yet been described during human locomotion.

Therefore, the purpose of this study is to determine whether interlimb reflexes serve to coordinate the body during walking. Muscle activity will be recorded from all extremities simultaneously during electrical nerve stimulation to cutaneous nerves located in the hand and foot during walking. Joint kinematics will also be recorded from both the upper and lower extremities to answer whether these reflexes serve a functional role during locomotion.

CHAPTER 2 - Review of Literature

During locomotion, it is imperative that the limbs are coordinated. The limbs must be coordinated in order to produce efficient locomotion and for the preservation of balance. Reflex components are one way that the body achieves this coordination (Zehr & Stein, 1999). They are organized in such a way to help us deal with unexpected occurrences that may occur during locomotion. Specifically, reflexes allow us to maintain postural stability that could be compromised while encountering a perturbation (e.g. due to encountering a raised crack in a sidewalk during walking). A great deal of research has helped us gain a good understanding of how responses within the legs are coordinated during a stumble. However, there is not much known about the function of interlimb reflexes, which are defined as responses occurring in the muscles of unstimulated limbs. The mechanisms and possible functional relevance of these interlimb connections are not well understood. This section of my thesis will review the body of literature that exists on this phenomenon, which has received considerable attention in animals. The limited number of studies that have been done on humans will also be discussed.

Animal studies

Sherrington (1910) made the first observation of interlimb reflexes in cats. He noted motor responses in the hindlimbs of both decerebrate (transection of the brainstem at the midbrain) and high-spinalized (transection of the spinal cord) cats could be elicited by stimulating an afferent nerve in the forelimb. The motor

responses observed resembled a basic pattern of stepping movements of all four limbs. In the cat, the coordination of the forelimbs and hindlimbs is necessary for gait, and a great deal of literature has focused on this interlimb coordination (English, 1979, 1980, 1985; Halbertsma, 1983; Lloyd, 1942; Miller et al., 1975; Schomburg et al., 1978b). However, the system linking these forelimb-hindlimb responses was not further investigated until sometime after Sherrington's work.

Lloyd (1942) later showed that a descending propriospinal system could account for the transmission of these reflexes from the forelimb to the hindlimb. He showed this by stimulating the brachial plexus, which produced an inhibition on lumbosacral motor pools. The propriospinal system consists of neurons that connect distant segments of the spinal cord (Ghez, 1991). Skinner et al. (1980) provided more evidence for long propriospinal cells being involved in transmitting interlimb reflexes from the forelimb to the hindlimb. They showed that long descending propriospinal neurons (having their somas located in the cervical enlargement of the spinal cord, and projecting their axons as caudal as L2) became activated with stimulation of the tactile, thermal, and joint receptors in the forelimb. Since long descending propriospinal cells received input from various receptors in the forelimb, the authors suggested that these cells could transmit afferent information regarding forelimb position and weight-bearing to the lumbosacral portion of the spinal cord. Therefore, long descending propriospinal neurons, connecting the lumbar and thoracic segments of the spinal cord, have been suggested as functioning in interlimb coordination, and

would thus be active during quadrupedal gait (Alstermark et al., 1981; Skinner et al., 1980).

Another study by Gernandt and Mergirian (1961) shed further light onto the mechanism mediating interlimb reflexes by showing an ascending propriospinal system, which could also conduct signals from the hindlimbs to the forelimbs. Additionally, they showed that in cats spinalized at C1 (in which only propriospinal connections remain), no interlimb reflex activity in the forelimb could be seen. This provided strong evidence that regions above C1 must be either directly or indirectly involved in interlimb transmissions of signals from hindlimbs to forelimbs.

English (1980) attempted to identify the neural pathways that are associated with the coordination of the forelimbs and hindlimbs during gait. He found that lesions to the dorsal columns at T12 had little to no effect on the coordination of the homonymous limbs (i.e. forelimb-forelimb and hindlimb-hindlimb coordination), but had a profound effect on the pattern of the step cycles of interlimb coordination (i.e. between the forelimb and hindlimb) during gait. Specifically, the step cycles of the forelimbs and hindlimbs were altered to include more frequent coupling of the homonymous limbs. However, lesions made to the dorsal columns at C2-C3 produced very minor effects on interlimb coordination. It was thus proposed that neurons located in the caudal thoracic, but not the cervical portion of the dorsal columns, were involved in the coordination of the forelimbs and hindlimbs. However, there are several tracts that exist in the dorsal columns. English (1980) suggested there could be three

systems within the dorsal columns that could play a role in interlimb coordination: the dorsal spinocerebellar tract (DSCT), the secondary dorsal column neurons, and dorsal long propriospinal pathways.

To answer this question, English (1985) studied the possible role of the DSCT in interlimb coordination. This tract provides the cerebellum with information pertaining to hindlimb proprioceptor activity during gait in decerebrate cats. It was thought that if the DSCT did play a role in interlimb coordination, a lesion to this tract would cause a change in the pattern of this coordination, since there would be no connection to the cerebellum. This would cause the cerebellum to alter its output to the limbs during locomotion. Lesions (at T6) of the DSCT produced almost the same minimal change in pattern of coordination between the forelimbs and hindlimbs as that seen with lesions of the cervical portion of the dorsal columns (English, 1980). The evidence provided by English (1985) suggested long ascending propriospinal neurons in the dorsal columns, and not the DSCT or the secondary dorsal column neurons, were responsible for interlimb coordination. At the level of the lesion, long ascending propriospinal neurons are the only one of the three systems in the dorsal columns remaining.

In summary, studies done on cats suggest that interlimb reflexes between the forelimbs and hindlimbs are mediated by long propriospinal neurons. These neurons link the lumbar and thoracic portions of the spinal cord. Additionally, it seems that this pathway mediates interlimb reflexes in the rostral and caudal directions.

Interlimb reflexes assist in coordination during locomotion

There is a general consensus that interlimb reflexes exist in the cat. However, the results of studies investigating the possible functional relevance of these connections have been somewhat ambiguous. Miller et al. (1973a) showed that in high spinal cats (spinalized at C1), ascending propriospinal pathways originating from the lumbosacral cord could mediate excitatory and inhibitory changes in the reflexes to different populations of motoneurons innervating the forelimb muscles. By electrically stimulating hindlimb nerves, reflex responses were elicited in forelimb motor nerves. Monosynaptic reflexes in the pectoralis major and motoneurons innervating the flexor muscles of the forelimb were facilitated by hindlimb nerve stimulation. Ipsilateral hindlimb nerve stimulation was more effective in eliciting the response than contralateral stimulation. The short latencies (< 10 ms) of the facilitation of the reflexes seen in the pectoralis major motoneurons support the idea that some long ascending fibres within the spinal cord may make direct monosynaptic connections via a propriospinal interneuron on the motoneurons innervating this muscle. It was hypothesized that the propriospinal pathways in the spinal cord could serve as links between various segmental neuronal systems controlling the neck, limbs, and trunk, thus providing coordination of various parts of the body in complex movements.

It has been observed in normal cats trained to walk on a treadmill that, at varying speeds, the onset of the first extension of the hindlimb during its swing phase is followed 40 ms later by flexion of the ipsilateral forelimb at the end of its stance phase (Miller et al., 1973b). In a task such as stepping during walking, the

role of the ascending propriospinal pathways could be to contribute to forelimb flexor facilitation once the ipsilateral hindlimb has commenced its extension. This coupling of the ipsilateral limbs is the prevailing pattern in alternate stepping (i.e. walking), and this pattern of facilitation was also found in spinalized cats (Miller et al., 1973a).

Additionally, Miller et al. (1973b) showed that ascending long propriospinal pathways facilitate flexion of the forelimb, as previously found by Lloyd and McIntyre (1948). However in addition to this observation, it was shown that descending long propriospinal pathways facilitate extension of the hindlimb. This could serve to reinforce hindlimb extension during the forelimb swing phase.

Work by Schomburg et al. (1975) led to the physiological discovery of the existence of an inhibitory descending propriospinal pathway, terminating at the motoneurons of the flexor digitorum longus in the hindlimb. A follow-up study by Schomburg et al. (1978b) proposed that a possible function of this pathway could be to inhibit plantar flexion of the toes during the hindlimb stance phase of locomotion. Such a movement is usually seen at the end of the stance phase, during the transition to the swing phase.

Intrasegmental crossed-reflexes during locomotion

Another feature of interlimb reflexes that has been observed is the phenomenon of phase-dependent modulation, which is the changing of the size or sign of a reflex depending on the phase of the during which the reflex is elicited. Grillner and Rossignol (1978) observed the hindlimb behaviour of

walking cats spinalized at T12. In about 60% of the cats tested, it was observed that if the superficial peroneal nerve in one of the hindlimbs was electrically stimulated while in the stance phase, and the contralateral limb was passively placed in flexion, a strong extension occurred in the contralateral limb. However, if the contralateral limb was extended at the time of stimulation, a crossed flexion occurred. Thus, the reflex response that a limb displays to a contralateral stimulus is dependent on its initial position. It was further hypothesized that this response could be a way in which the cat reacts to noxious stimuli during locomotion to maintain stability. Other studies have also shown the existence of this phenomenon (Forssberg et al., 1975, 1977). Such a reversal of the reflex response is probably dependent on a spinal central pattern generator (CPG) regulating these responses, since the descending drive from higher centres does not exist in spinalized cats. Further evidence for a spinal CPG intervening in locomotion came from Schomburg et al. (1977; Schomburg & Behrends, 1978a), who showed that phase-dependent conduction in excitatory descending propriospinal reflex pathways existed in spinalized cats that exhibited fictive locomotion.

Another paradigm used to study interlimb coordination involves altering the normal locomotor pattern by introducing some form of perturbation and observing how the cat adapts. It has been shown that the mechanism by which interlimb coordination is mediated is quite flexible, allowing for compensatory movements of the limbs in response to a perturbation during locomotion. Experiments using split-belt treadmills have been used with spinal cats

(Forssberg et al., 1980, Halbertsma, 1983). Spinal cats have been reported to adapt to this variation in belt speeds by increasing the duration of flexion of the limbs on the fast belt, and shortening the time for the swing phase in the limbs on the slow belt (Forssberg et al., 1980). It was proposed that afferent information about the movement is required to produce this interlimb coordination.

This idea has been supported by limb deafferentation studies (i.e. transection of the dorsal roots innervating the limb). Grillner and Zangger (1984) observed significant deterioration of interlimb coordination between the hindlimbs during walking following unilateral deafferentation in cats. As well, Guilani and Smith (1987) observed weaker coupling between the hindlimbs after deafferentation of a hindlimb of a chronic spinal cat. They also found the hindlimbs were not moving properly in phase with each other; the intact hindlimb was stepping at a faster frequency compared to the deafferented hindlimb.

In summary, the neural control of interlimb coordination in animals has been well documented. Stimulation of either forelimbs or hindlimbs produces reflex responses in the opposite homologous limbs. It appears that interlimb coordination during locomotion is capable of adapting to unexpected perturbations. It has also been shown that intraspinal components, such as long propriospinal cells, are fundamental for the transmission of signals between the forelimbs and hindlimbs. Supraspinal centres apparently govern the fine-tuning of these interlimb responses, but are not necessary for the transmission between the limbs. Furthermore, evidence also suggests the existence of a spinal CPG, producing phase-dependent interlimb reflex responses during gait. Afferent

information during gait appears to be essential for the triggering interlimb response to assist in limb coordination during quadrupedal gait.

Human studies

Static conditions

Reports of interlimb reflexes in humans have been somewhat limited in number. One of the first studies was done by Kearney and Chan (1979), who evoked interlimb reflexes in the arm muscles via cutaneous stimulation of the foot. They found that electrical stimulation of a cutaneous nerve in the ankle produced a response in the electromyography (EMG) of the ipsilateral biceps and triceps brachii, of which the earliest mean latencies were 91 and 92 ms respectively. In a later study, the authors evoked interlimb reflexes in the arm muscles by displacing the ankle (Kearney & Chan, 1981). Dorsiflexion of the ankle evoked a reflex response in triceps brachii, with the earliest mean peak latency being 55 ms. When the ankle was plantar flexed, evoked responses were recorded in both biceps and triceps brachii, where the onset of the earliest responses occurred at 51 and 54 ms respectively. Small ankle displacements resulted in interlimb reflexes that were larger in amplitude and of shorter latency compared to interlimb reflexes evoked by cutaneous stimulation. Kearney and Chan (1981) suggested that these differences in amplitude and latency between the two forms of stimuli (displacement and electrical stimuli) could be possibly due to connections of muscle afferents being stronger and more direct than cutaneous afferents.

Interlimb reflexes that have been evoked from the arm have been studied as well (Gassel & Ott, 1973; Marsden et al., 1978; Piersiur-Strehlow & Meinck, 1980; Traub et al., 1980). In the Marsden et al. (1978) experiment, subjects were asked to kneel and perform flexion of one elbow at a constant rate against a load attached to the wrist, while steadying themselves by holding a table top with the other arm. During this task the load was unexpectedly altered. They found that this alteration in load caused reflex responses to be evoked in the biceps and triceps of the contralateral arm. These responses were compensatory in nature because they resulted in keeping the body steady, and also prevented the body from swaying after the change in load. The authors concluded that these postural responses in the contralateral arm were due to afferent input from the perturbed arm activating cerebral mechanisms, thereby causing contractions of the distant postural muscles.

Traub et al. (1980) examined postural responses in the muscles of the legs while displacing the arm unexpectedly in both neurologically intact subjects and Parkinson's disease patients. Ipsilateral triceps surae responses began about 80 ms after the perturbation to the arm, but no actual movement of the leg was apparent until 150 ms in neurologically intact subjects. In other words, the response could not be due to the stretch of the triceps surae, since the reflex response preceded any detectable leg movement (i.e. a stretch of the muscle), and the latency for the functional stretch reflex in calf muscles is about 120 ms (Jones & Watt, 1971). Intravenous regional anesthesia was also done in one of the neurologically intact subjects to confirm the evoked EMG response from the

triceps surae was not due to stretching of the triceps surae. This technique produced mild paresthesia of the foot and eliminated the tendon jerk response in triceps surae. As a result, no change was found on the anticipatory postural response, thus confirming that these responses were not mediated by a possible stretch reflex from the triceps surae. Also, the sign of the response seen in the triceps surae muscles was dependent on which direction the arm was perturbed. Specifically, if the arm was pulled forward the EMG activity of the triceps surae increased, reducing the forward sway of the body due to the arm perturbation, and vice-versa. This was consistent with the findings of Kearney and Chan (1981), who also showed the interlimb reflex in the triceps brachii was dependent upon which way the ankle was displaced.

The findings from the neurologically intact subjects (Traub et al., 1980) support the conclusion made by Marsden et al. (1978) that these reflex responses in the triceps surae originated from the perturbed arm and that the afferent input was not cutaneous in nature. Taken together, these findings support the notion that the descending reflexes linking the activity of ankle muscles to arm displacement are probably organized in a similar manner to ascending reflexes linking ankle displacement to arm muscle activity.

Sarica and Ertekin (1985) stimulated the median nerve in neurologically intact subjects and intrathecal recordings were made from the intervertebral subarachnoid space between T10 and T12. They found electrical stimulation of the median nerve elicited descending lumbosacral potentials (DCLP) in the spinal cord. From the short onset latency of the DCLP (~12 ms), the authors concluded

that the DCLP were due to an ipsilateral fast-conducting propriospinal descending pathway originating from the stimulated arm. This pathway could allow for the rapid transmission of afferent information from the upper extremity to the lumbosacral cord, which would have implications for interlimb reflex responses involving posture and gait.

Interlimb reflexes between the upper and lower extremities were investigated by Calancie (1991) in neurologically intact subjects and in subjects with cervical spinal cord injury (SCI). Interlimb responses were evoked in the upper extremity muscles by electrically stimulating lower extremity mixed nerves. The key finding was that no interlimb responses were seen in the neurologically intact subjects or the SCI subjects that had recovered significant voluntary motor function in at least 2 levels caudal to the initial level of paralysis since hospital admission ("motor-incomplete" quadriplegics). The only subjects that exhibited interlimb reflexes were those labeled "motor-complete" quadriplegics (those having made minor gains in muscle strength at the level or one level caudal to the injury site). Interlimb reflexes in these subjects were seen in both the ipsilateral and contralateral arm muscles, mainly the intrinsic hand muscles. Since these interlimb reflexes could not be evoked in motor-incomplete or neurologically intact subjects, a supraspinal or central contribution to these responses was not likely. The author therefore suggested that his findings were due to the spinal cord acting in isolation from any descending influence, and that long ascending propriospinal neurons in the spinal cord were responsible for transmitting the signal from the lumbar cord to the cervical cord.

Another study investigating the role of cutaneous stimulation in evoking interlimb reflexes was done by Calancie et al. (1996), who showed that cutaneous stimulation at the lower extremities can also cause the recruitment of upper limb motor units in motor-complete subjects. The system implicated for these cutaneous effects was the spinocervical tract, as it has been seen in cats that this tract has extensive convergence from various afferent fibres (Cervero et al., 1977; Downie et al., 1988).

Zehr et al. (2001a) studied interlimb reflexes using cutaneous nerve stimulation as well, but in neurologically intact subjects. Electrical stimulation of the superficial peroneal nerve in the foot, and the superficial radial nerve in the hand (both cutaneous nerves) produced large, reproducible interlimb reflexes that were also widespread. This suggested that there were strong interlimb cutaneous reflex connections between the cervical and lumbar regions of the spinal cord. Also, the early latency reflexes were very short (< 70 ms), which suggested that a propriospinal pathway mediates them, with little possibility of supraspinal influence.

One difference in the methodology between the Zehr et al. (2001a) and Calancie (1991) studies is the latter study evoked interlimb reflexes by stimulating mixed nerves (i.e. median, tibial, and common peroneal nerves), as opposed to cutaneous nerves (superficial peroneal and superficial radial). Calancie et al. (1996) suggested that a different pathway than that elicited by mixed nerve stimulation could mediate interlimb reflexes elicited by cutaneous nerve stimulation. In other words, the superficial peroneal and superficial radial

nerves may have different projections between them that involve interlimb pathways. In addition, the methodology described by Calancie (1991) was not very detailed, as there was little mention of the procedures and results for the neurologically intact group. This makes it difficult to compare the observations between studies.

A paper by McIlroy and Maki (1995) reported a short latency response in the posterior deltoid as a result of platform translation (i.e. perturbation) in varying directions and in varying magnitudes. The perturbation did not cause any noticeable movement of the arm, as measured by shoulder and elbow kinematic data, thus these responses could not be due to the stretch reflex (Ia afferent output). The response was also not attributable to a startle response, as the response recorded was related to the degree of the perturbation, and the observed response persisted as trials went on. Subjects undergoing a series of perturbations would gain a sense of familiarity with the perturbation, causing a reduction of the magnitude of the startle response over time. Functionally, the activation of posterior deltoid is not likely associated with counterbalancing the body, as the arm movements elicited by the perturbation were similar regardless of the direction of the translation of the platform. The authors indirectly suggested that the responses seen in the posterior deltoid might have arisen from the lower limbs. However, the notion that the vestibular system may potentially contribute to the responses observed was also mentioned. Studies involving mechanical perturbations cannot exclude this system from playing a role in any reflex responses seen. For this reason and others, electrical stimulation is used to

activate cutaneous nerves that innervate portions of the skin that would be in contact with a physical obstacle, which would usually cause a perturbation.

Delwaide and Crenna (1983, 1984) found that stimulation of the sural nerve (cutaneous nerve) in the leg resulted in the facilitation of muscles in a rostrocaudal progression (i.e. masseter, followed by arm muscles, then leg muscles). The authors postulated that the presence of a supraspinal centre activated by afferent inflow resulted in the rostrocaudal pattern of facilitation observed. However, this was only a postulation, and only focused research will provide a better understanding to the mechanisms governing these responses.

Responses during locomotion: coupling between the legs

Most of the studies that have examined interlimb reflexes in humans have done so under static conditions, using displacements of the arm and leg, as well as electrical stimulation to elicit the reflex responses. However, little research has been conducted investigating interlimb reflexes during human locomotion. Studying interlimb reflexes during walking may provide insight as to whether they serve a functional role. Berger et al. (1984) conducted a study in which EMG responses from the muscles of the lower leg were recorded following a perturbation to a limb during walking. The authors found that by delivering a perturbation via electrical stimulation of the right tibial nerve during swing, a prolongation of contralateral stance was obtained. This showed the existence of coupling between the duration of ipsilateral swing and contralateral stance during locomotion.

A study by Van Wezel et al. (1997) used electrical stimulation to stimulate the sural, posterior tibial, and superficial peroneal nerves (cutaneous nerves with different innervation areas of the foot) during walking. Surface EMG was recorded from muscles of both the stimulated and unstimulated legs. It was found that in the stimulated leg, the phase-dependent reflex responses were nerve-specific. A lesser degree of nerve specificity was also shown in the unstimulated leg. The authors concluded that differentially controlled reflex pathways mediated these nerve-specific responses for each of the three nerves. Zehr et al. (1997) also induced reflexes by electrical cutaneous stimulation of the superficial peroneal nerve during walking, however surface EMG was only recorded on the stimulated leg, along with knee and ankle kinematics. With stimulation, tibialis anterior showed an inhibitory response during the swing phase, which correlated with ankle plantar flexion. Also, biceps femoris and vastus lateralis showed excitatory responses throughout swing, and these responses were correlated with knee flexion during early swing. Taken together, the authors argued a functional role for these responses; they were indicative of a stumbling corrective response. In brief, this response allows for the body to avoid a stumble upon encountering a perturbation, while simultaneously allowing the body to continue its forward progression. These two studies showed that cutaneous nerve stimulation evoked responses that were nerve specific, and that the control of these responses is ongoing throughout the walking cycle.

Responses during rhythmic movement: coupling between the arms

Interlimb reflexes between the upper extremities were partly investigated by Zehr and Kido (2001) during rhythmic arm cycling. Electrical cutaneous stimulation was delivered to the median, ulnar, and superficial radial nerves. Surface EMG was mainly focused on the stimulated arm, but EMG was also recorded from the anterior and posterior deltoid in the unstimulated arm. They reported reflexes in the anterior deltoid of both arms. Interestingly, the pattern of reflex modulation seen in the anterior deltoid of the unstimulated arm was reciprocal to that observed in the same muscle of the stimulated arm during the early, middle, and late portions of the arm-crank cycle for all three nerves.

Locomotor responses: coupling between the arms and legs

The prevalence of interlimb reflexes between the upper and lower extremities has not been greatly investigated during human walking. A study was conducted by Quintern et al. (1985), in which reflex responses in the arm were elicited by inducing gait perturbations in humans. With successive trials, the response gradually diminished. Reflex responses were elicited in the ipsilateral deltoid muscle, with a onset latency of less than 100 ms. Cortical potentials were also recorded in conjunction with EMG from the deltoid, and the activity patterns of these two recordings were closely matched, thus suggesting a transcortical mechanism mediating these responses. The authors briefly discussed the possible functional significance of the interlimb reflex response seen in the deltoid muscle, and interpreted it as a protective response during gait

perturbations, in which the body unconsciously performs an arm extension movement in preparation for a possible fall forward. The reason for this response diminishing as the trials progressed was due to the subjects gaining familiarity with the perturbations.

Wannier et al. (2001) investigated the coordination between the upper and lower extremities during various forms of locomotion (walking, crawling, and swimming). They found that during every form of locomotion, the arm and leg moved in such a way that interlimb coupling occurred across the trunk. This means that the arms and legs are coordinated not only during walking, but also in other locomotor tasks. The authors attributed the coordination to a system comprised of two coupled oscillators (i.e. central pattern generators), one each for the arms and legs.

Further providing evidence for the existence of this system in humans comes from the work by Dietz et al. (2001), who observed distinct bilateral arm muscle responses with electrical stimulation of the distal tibial nerve and small leg displacements during walking. Also of interest was the finding that the responses were not present during standing while swinging the arms, or while sitting. The observations suggested the existence of a flexible, task-dependent neuronal coupling between the arms and legs. Additionally, it was suggested that a central pattern generator gates the pathway involved with coupling arm and leg movements during walking (for review, see Dietz, 2002).

The phenomenon of interlimb reflexes in humans has not been thoroughly investigated. What we do know about interlimb reflexes arises primarily from

studies done on cats. The pathways by which these responses are mediated via the spinal cord have been well documented in these types of studies, however the picture is not as clear in humans. Further research in humans needs to be conducted to examine the mechanisms mediating these reflexes.

CHAPTER 3 - Methods

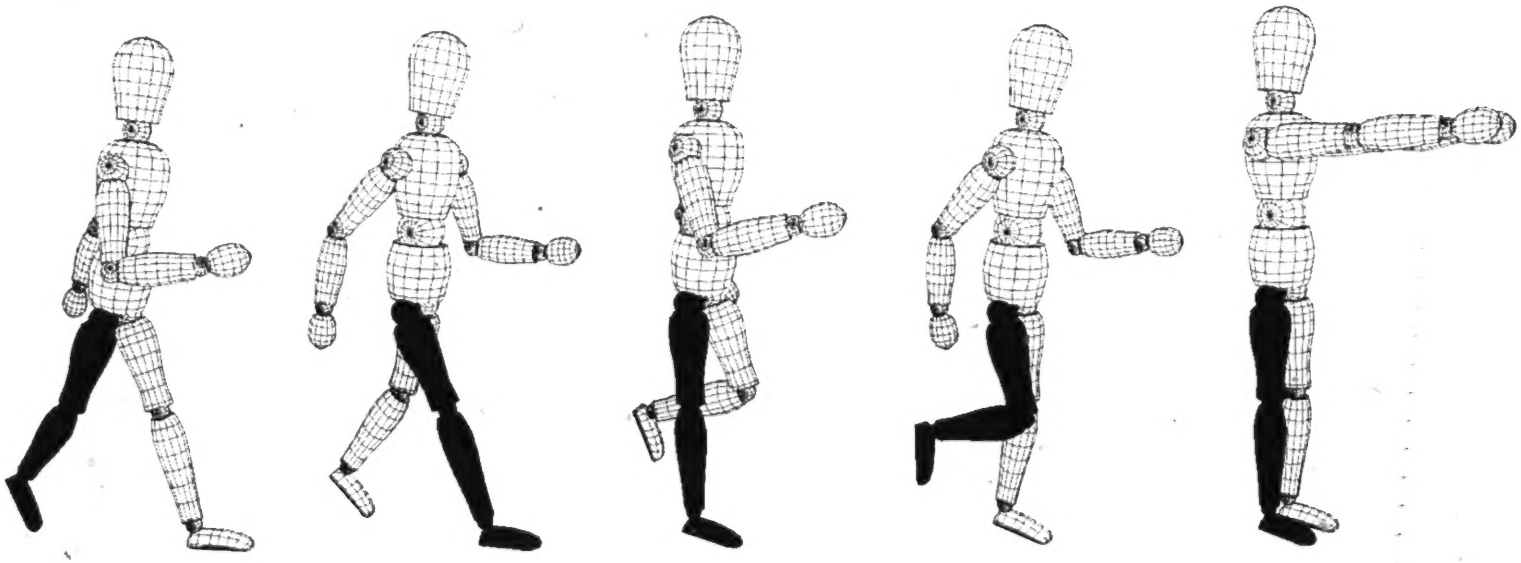
Terminology

The term interlimb reflex is used to describe reflexes in muscles that are located in unstimulated limbs (see Zehr et al., 2001a). For example, while stimulating the right superficial peroneal nerve, reflexes in muscles in any of the limbs except for the right leg are interlimb reflexes. Muscles are described as ipsilateral (i) or contralateral (c) with respect to the site of stimulation. In all experiments, nerve stimulation was delivered to the right side of the body.

Subjects and protocol

Subjects between the ages of 18-34 years participated with informed, written consent in a protocol approved by the Human Research Ethics Board (Health Research) at the University of Alberta. Sixteen subjects participated in the superficial peroneal (SP) nerve stimulation protocol, and fifteen in the superficial radial (SR) nerve protocol. All subjects were free of documented neurological impairment. Subjects were asked to maintain five different static body postures, each lasting approximately one minute in duration, while standing on a stationary treadmill (Fig. 1). Four of these postures mimicked body postures during key points in the step cycle (late stance, early stance, midstance, midswing). This was done to determine if the stimulus intensity was adequate to elicit a reflex, and also to compare reflexes evoked during similar postures achieved during walking. The remaining fifth posture was used to activate the

Figure 1: Schematic illustration of the five static body held by subjects on the treadmill.



muscles of the arm bilaterally. Subjects then walked on a motorized treadmill at 3 mph for 20 minutes. Approximately 1200 steps were collected during the walking task (including both stimulated and unstimulated (control) steps). This procedure was performed for each nerve stimulation condition.

Nerve stimulation

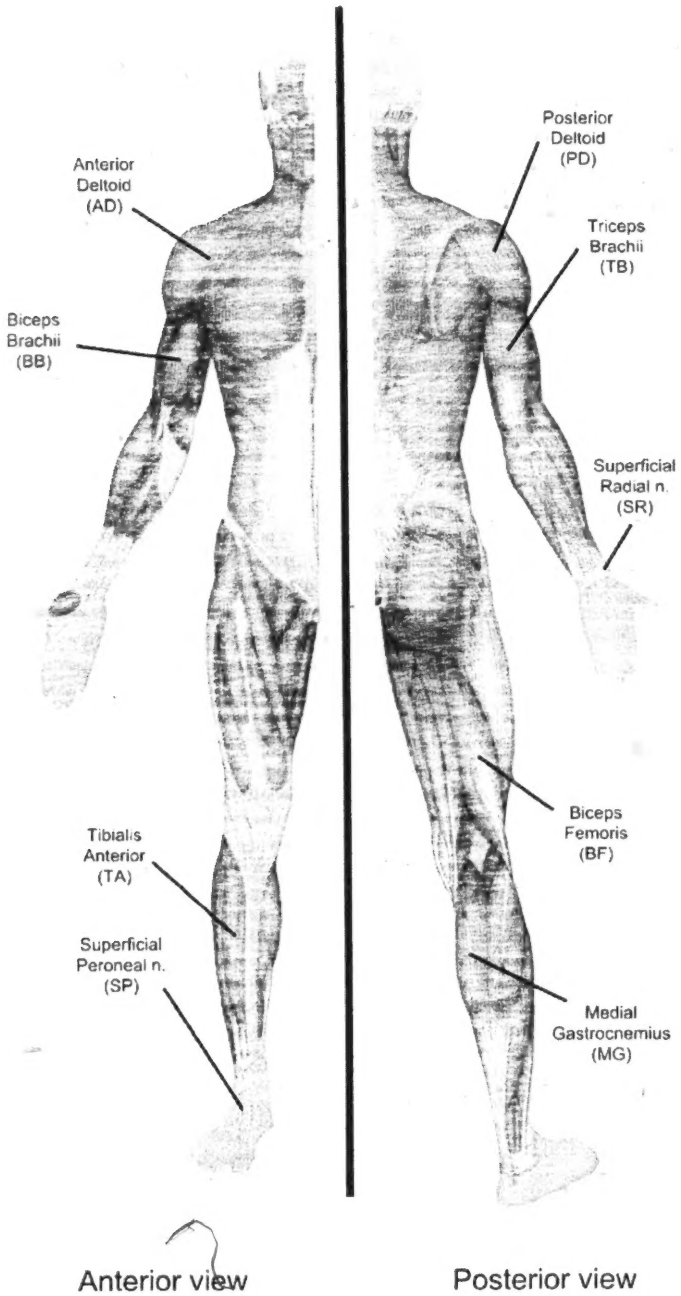
Cutaneous reflexes were evoked by using trains (5 × 1.0 ms pulses @ 300 Hz) of isolated constant current stimulation (Grass S88 stimulator with SIU5 and CCU1 isolation and constant current units, AstroMed-Grass Inc.) applied to the SP or to the SR nerve using flexible 1 cm disposable surface EMG electrodes (H69-P, Jason-Kendall LTP, CA). Electrodes for the SP nerve were placed in a bipolar configuration on the anterior surface of the leg near the crease of the ankle joint, and for the SR nerve, the dorsal surface of the hand (near the anatomical snuff box, just proximal and distal to the styloid process of the radius). For each of the five static posture trials, stimulation was delivered approximately once every 1.5 seconds. During the walking trial, the stimulation was delivered pseudorandomly via a pulse generator, with a minimal repeat time approximately equal to the step cycle duration and a maximum that was approximately twice this duration. This resulted in a stimulus delivered once every 2-4 seconds, and no more than one stimulus was given per step cycle. Stimulus intensity (mean of the maximum output of the stimulator expressed as a percentage ± SEM) was set as a multiple of the threshold at which a clear radiating paresthesia (radiating threshold, RT) into the innervation area of the nerve was reported. The

innervation area of the SP nerve is the dorsum of the foot, and for the SR nerve, the dorsolateral portion of the hand. It is thought that the RT value corresponds to the activation of fascicles in the cutaneous nerve under the stimulation electrodes (Zehr et al., 1997). These two nerves were chosen partly due to findings in previous studies that showed prominent reflexes in muscles of the stimulated limbs during rhythmic human arm (Zehr & Chua, 2000) and leg (Zehr et al., 1997) movement. Additionally, interlimb reflexes arising from the stimulation of these nerves have been studied during static tasks (Zehr et al., 2001a). Stimulation intensities were set to evoke a strong cutaneous sensation (during standing) that was not deemed painful by the subjects. This level ranged from 2-4 × RT (3.34 × RT ± 0.19 for SP, 3.0 × RT ± 0.28 for SR).

Electromyography (EMG)

Once the skin was abraded and cleaned with alcohol, disposable 1 cm surface EMG electrodes (H69-P and H59-P, Jason-Kendall LTP, CA) were applied in a bipolar configuration over the tibialis anterior (TA), medial gastrocnemius (MG), biceps femoris (BF), anterior deltoid (AD), posterior deltoid (PD), long head of biceps brachii (BB), and long head of triceps brachii (TB) muscles bilaterally (Fig. 2). Ground electrodes were placed over electrically neutral tissue. EMG signals were preamplified and bandpass filtered at 100-300 Hz (P511 Grass Instruments, AstroMed, Inc.).

Figure 2: Anatomical locations of human muscles and nerves referenced in the text.



Kinematics and step-cycle detection

Data on the kinematics of the ankle and elbow joints were recorded bilaterally in all subjects using bi-axial electrogoniometers (Biometrics Ltd., Cwenfellinfach, Gwent, UK) placed over the joint, secured with 2-sided plastic tape and fabric straps. Additionally, in six subjects, kinematic data were also recorded from the knee and shoulder. For the ankle joint, the bi-axial goniometers were placed with the distal end on the lateral side of the heel and the proximal end fixed to the lower leg, above the lateral malleolus. Kinematic data from the shoulder were recorded by placing goniometers over the acromion and the upper arm (lateral side). For the other joints, the goniometers were placed on the lateral side of the joint. Step-cycle parameters (e.g. heel contact, toe-off) were obtained with the use of custom-made force sensors, located in the insole of the subject's right shoe.

Data acquisition and analysis

All data were sampled at 1000 Hz with a 12 bit A/D converter connected to a Pentium III 500 MHz microcomputer running custom-written (Dr. Romeo Chua, University of British Columbia) LabView software (National Instruments, Austin, TX). For the walking task, custom-written software programs (Matlab, The Mathworks, Natick, MA) were used to separate the step cycle into sixteen equal parts (portions), beginning with heel contact. The stimuli occurred randomly throughout the step cycle. During offline analysis, the EMG signals were full-wave rectified and filtered (see below). For each bin, the average trace from the

unstimulated steps was subtracted from the corresponding stimulated average trace. This produced a subtracted evoked EMG trace for each subject. From this, the stimulus artifact was removed, and the EMG trace was then filtered using a dual-pass 4th order Butterworth low-pass filter at 40 Hz. This EMG was then analyzed for the net reflex effect using the average cumulative reflex EMG 150 ms poststimulus technique ($ACRE_{150}$; see Zehr et al., 1997), utilizing custom-written software. Briefly, the subtracted post-stimulus EMG trace for each subject was integrated up to 150 ms poststimulus, and this value was then divided by the time of integration to produce a net reflex (i.e. negative values equate to overall suppression; positive values indicate overall facilitation). Additionally, cutaneous reflexes (in the subtracted EMG traces) were examined at early (< 80 ms to peak), middle (80-120 ms to peak), and late (> 120 ms to peak) latencies. Only those reflexes that exceeded a 3-SD band (centred about the mean prestimulus EMG level) for at least 5 ms were analyzed. The amplitude of the reflexes was defined by the mean EMG value in a time window extending ± 5 ms from the peak. For inter-subject comparison, the $ACRE_{150}$ and cutaneous reflex amplitude values (baseline to peak) for each subject were normalized to the peak unstimulated EMG amplitude value occurring during the step cycle for each muscle, and were then expressed as a ratio.

For each of the static postures, fifty rectified EMG sweeps (100 ms pre- and 200 ms poststimulus) were collected using custom-written Labview software. The average sweep was then visually inspected for cutaneous reflexes using

custom-written software (Matlab, The Mathworks, Natick, MA) using the criteria identified above.

EMG activity during movement

In order to measure the level of EMG activity in the leg and arm muscles during walking, analysis was done on the control EMG across all 16 portions of the step cycle. To allow for the quantification of the background EMG patterns during the walking cycle, a modulation index ($MI = [(EMG_{max} - EMG_{min}) / EMG_{max}] \times 100$) was calculated for each muscle at each of the portions of the step cycle, as used previously for arm cycling movement (Zehr & Chua, 2000; Zehr & Kido, 2001). The MI value indicates the extent to which a muscle is rhythmically active throughout the step cycle.

Kinematic analysis

Subtracted values for changes in joint angle were obtained as described above for the EMG data. The maximum change observed over an interval of 120-200 ms poststimulus was calculated. This window, which is similar to one used previously (Zehr et al., 1997), was chosen to account for the delay between an EMG response and an observable mechanical change in joint angle. These values were normalized to the maximum range of motion recorded for each subject during the step cycle, and then expressed as percentages.

Statistics

In all cases, analysis was performed using the averaged normalized values for each subject from each part of the step cycle. A 1-way repeated-measures analysis of variance (RM ANOVA; 5 postures, subtracted EMG) was used to determine significant differences in the background EMG level between the postures. This test was also used to calculate differences between the postures for the early and middle latency cutaneous reflex amplitudes. A 2-way RM ANOVA (2 levels of EMG (stimulated, unstimulated), 16 portions of step cycle) was used to determine significant net reflexes, as well as early, middle, and late latency cutaneous reflexes for each part of the step cycle. This method of analysis was also used to determine whether kinematic changes were significant. Tukey's HSD test was used to post-hoc any significant main effects observed. Linear least-squares regression analysis was used to evaluate correlations between the net reflex values and changes in joint angle at each part of the step cycle for the muscles involved at a particular joint. Descriptive statistics included means ± standard error of the mean (SEM), and statistical significance was set at $p < 0.05$.

CHAPTER 4 - Results

The results of SP nerve stimulation on the reflexes and kinematics of the lower and upper extremities, as well as SR nerve stimulation on the reflexes and kinematics of the lower extremities will be noted in this section. The effects of SR nerve stimulation on the muscles and kinematics of the upper extremities are noted in another separate paper (Appendix A).

Background EMG patterns of leg and arm muscles during walking

Average background EMG values obtained from all subjects for both SP and SR nerve stimulation protocols across all of the 16 portions of the walking cycle are plotted in Figures 3 and 4. All lower extremity muscles are plotted in Figure 3, and muscles in the upper extremities in Figure 4, with the ipsilateral and contralateral muscles plotted in the left and right columns respectively. These values are expressed as a ratio of the maximal background EMG activity observed for each muscle. The background EMG modulation was very similar for each muscle across both nerves. The stance phase of the walking cycle for the ipsilateral side is portions 1-8, and the swing phase is portions 10-15. The stance-to-swing transition occurs in part 9, and the swing-to-stance transition in part 16. On the contralateral side, the stance phase occurs during portions 1 to approximately 2, and portions 8 to 16, while the swing phase occurs during portions 2 to 8. All portions of the step cycle are referenced to the position of each leg.

Figure 3: Normalized background EMG across the step cycle for muscles of the lower extremities. Values are averaged across all subjects for each nerve stimulation condition. Abbreviations are: TA, tibialis anterior; MG, medial gastrocnemius; BF, biceps femoris; SP, superficial peroneal nerve; SR, superficial radial nerve. i and c signify ipsilateral and contralateral (relative to the site of stimulation) muscles. Shown at the bottom right of each graph is the modulation index (MI, expressed as a percentage) value calculated for that muscle for each nerve stimulation condition. Values are normalized to the peak value during the walking trial for each subject for each stimulation condition.

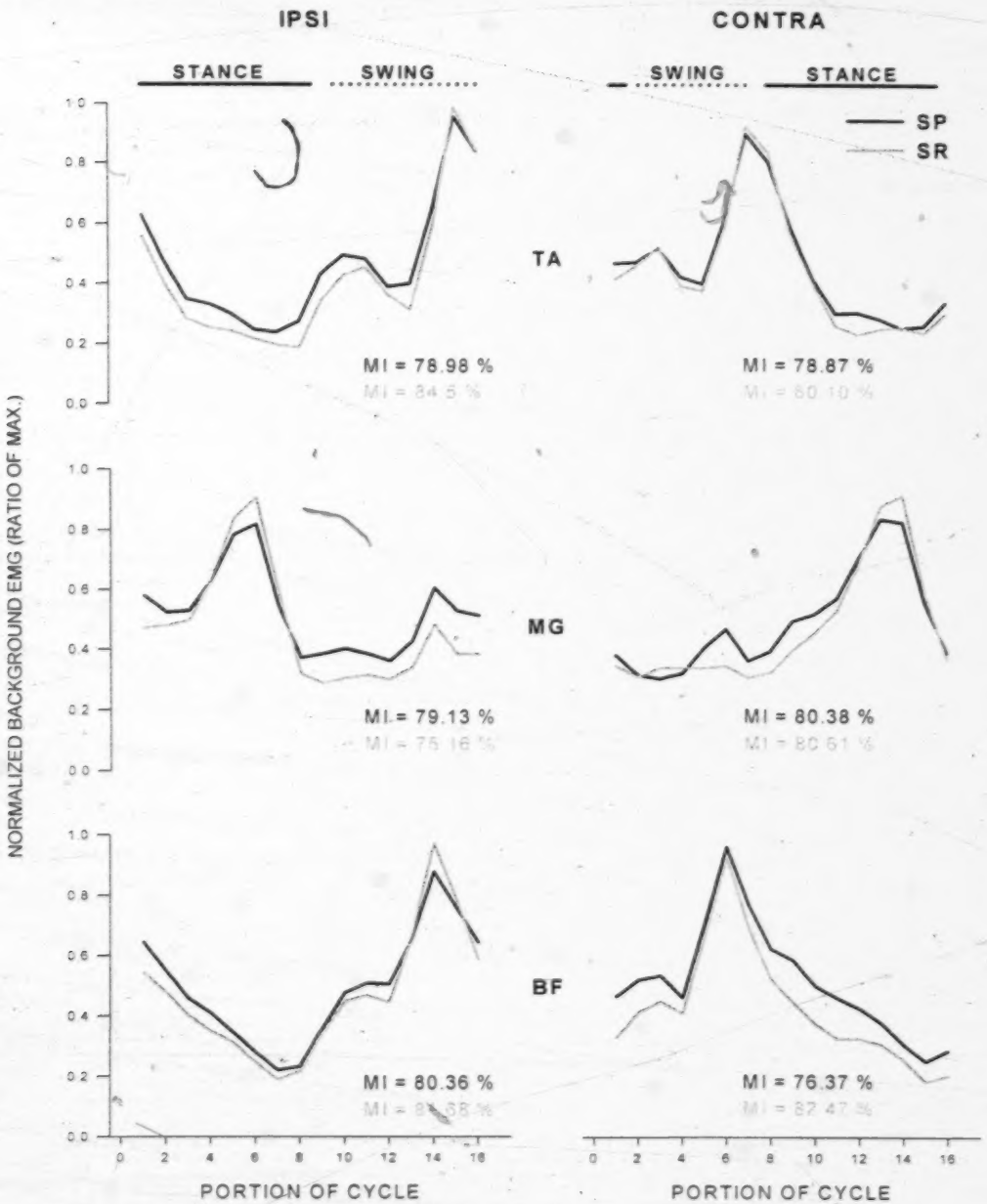
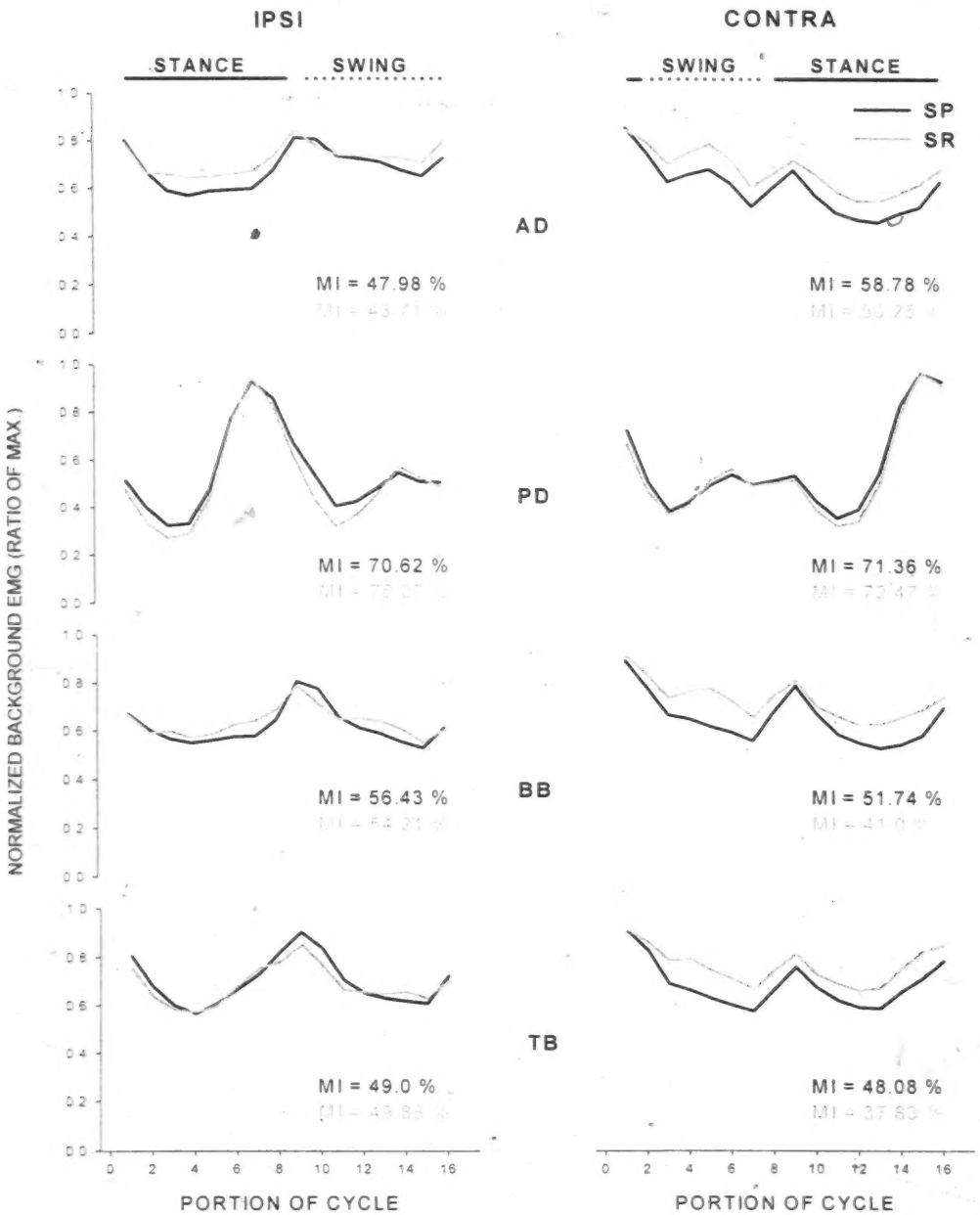


Figure 4: Normalized background EMG across the step cycle for muscles of the upper extremities. Values are averaged across all subjects for each nerve stimulation condition. Abbreviations are: AD, anterior deltoid; PD, posterior deltoid; BB, biceps brachii; TB, triceps brachii. All other abbreviations are as in Figure 3. Shown at the bottom right of each graph is the modulation index (MI, expressed as a percentage) value calculated for that muscle for each nerve stimulation condition. Values are normalized to the peak value during the walking trial for each subject for each stimulation condition.



Across all of the leg muscles, the amount of modulation was relatively the same as measured by the modulation index (MI). The MI values were between approximately 76 to 85 percent (Fig. 3). The background EMG activity was reciprocal in nature across the ipsilateral and contralateral leg muscles (e.g. peak background EMG activity during portions 5-6 in iMG; low activity in cMG during same portions). Reciprocal EMG activity was also observed across the ipsilateral and contralateral muscles of the upper extremities (Fig. 4). The largest modulation was observed in the PD muscles, with the ipsilateral side having an average MI value of 86.14% across both nerve stimulation protocols.

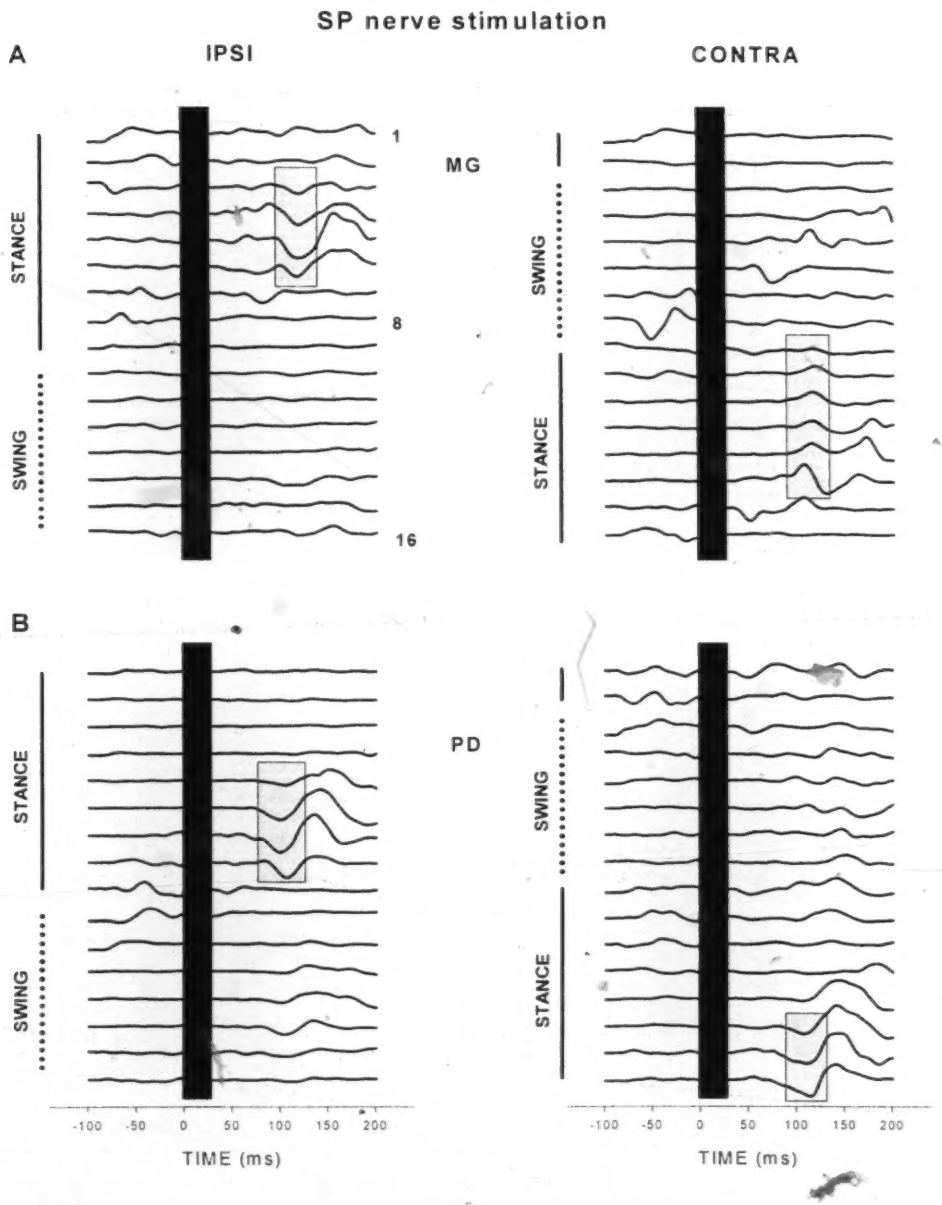
Responses to SP nerve stimulation during locomotion

Lower limb responses

Figure 5A shows subtracted EMG traces taken from one subject during SP nerve stimulation. Phase-modulation of cutaneous reflexes between the muscles of the lower limbs (i.e. between the ipsilateral and contralateral sides) was observed with electrical stimulation of the SP nerve during the step cycle. In Figure 5A, inhibition occurred during stance (portions 3-6) for iMG, whereas facilitation was observed in stance (portions 9-14) for cMG. The light gray vertical bar on the figure highlights these responses.

In all three lower limb muscles that were recorded, no significant responses were observed at the early latency reflex period (not shown). However, crossed effects (responses observed on both sides of the body) were noted between the ipsilateral and contralateral sides for the middle latency reflex

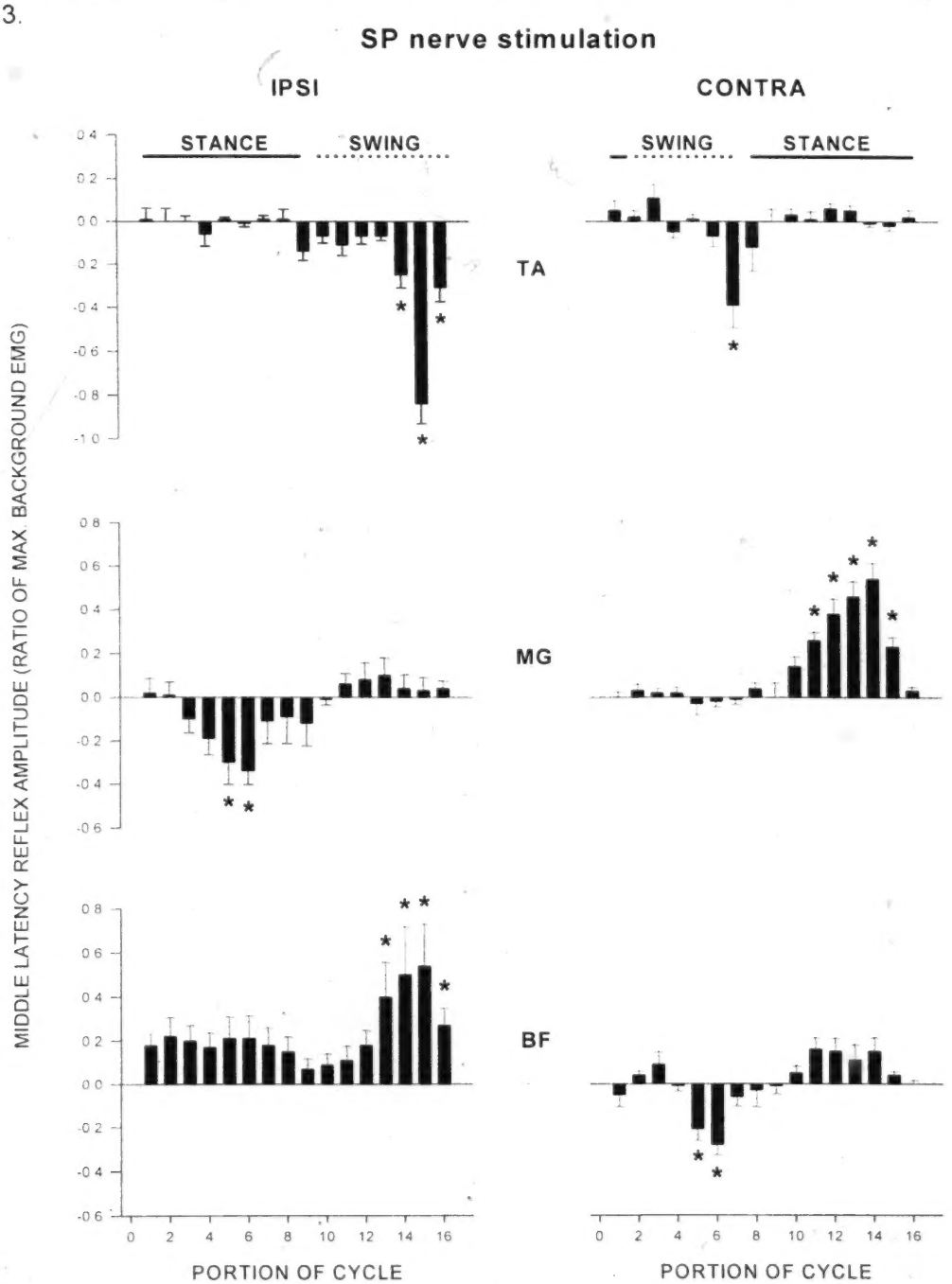
Figure 5: Subtracted EMG traces from one subject evoked by SP nerve stimulation during the step cycle. Top two traces are from iMG (left) and cMG (right) (A), while the bottom two traces are from iPD (left) and cPD (right) (B). The grey rectangle highlights the response observed during particular portions of the step cycle (portions indicated by the numbers to the right of each graph; 1 indicates ipsilateral heel strike). Note the reversal in sign of the reflex response between iMG (suppression) and cMG (facilitation) during the stance phase. Suppression is seen in both iPD and cPD during stance. Stimulus artifact has been removed from each trace, and replaced by a black vertical bar extending from time 0 out to approximately 30 ms poststimulus. Abbreviations are as in Figure 3.



period across all subjects. Figure 6 shows the amplitude of these middle latency responses for the lower limb muscles with SP nerve stimulation. In iTA (upper left of figure), a significant ($p < 0.05$) inhibitory response was seen during the latter portion of the swing phase, as indicated by the asterisks over portions 14-16, while in cTA (upper right) an inhibitory response is also seen at the same relative portion of the walking cycle (portion 7). While each leg was in the late stance phase of the movement cycle, iMG (middle left) showed a significant inhibitory response (portions 5-6), while facilitation was seen in cMG (middle right, portions 11-15). Facilitation was also observed during swing (portions 13-16) for iBF (lower left), whereas cBF (lower right) showed significant inhibition (portions 5-6) during the same phase. Note that in the ankle flexor TA, inhibition was observed bilaterally during swing. However in MG and BF, a reciprocal crossed effect was observed, with iMG exhibiting inhibition during stance (portions 5-6), while cMG displayed a facilitation response during the same phase. This reversal in sign was also seen in BF, with facilitation occurring in iBF and inhibition in cBF during swing.

The overall net reflex ($ACRE_{150}$) was also calculated (not shown). Within the muscles of the lower limbs, significant ($p < 0.05$) inhibition was observed in iTA during late swing (just before heel contact), while facilitation occurred in the same part of the step cycle for iBF. The response in cMG was also a significant facilitation during late swing (not shown).

Figure 6: Middle latency (80-120 ms poststimulus) reflexes for muscles of the lower extremities averaged across all subjects (n=16, means ± SEM) for SP nerve stimulation throughout the step cycle. Reflex amplitudes have been normalized to the peak value of the background (unstimulated) EMG obtained in the step cycle for each subject, and are expressed as ratios. Asterisks indicate effects significantly different from zero at $p < 0.05$. Abbreviations are as in Figure 3.



Task-dependency of SP nerve cutaneous reflexes in the lower limbs

Early and middle latency cutaneous reflex amplitudes were plotted against background EMG across the step cycle and for the five static postures, and linear regression analysis was performed. The Pearson correlation coefficients are shown in Table 1. Background EMG values for the lower limbs were similar between the two conditions. For the early latency period, no significant correlations were observed during the static postures.

Significant correlations between reflex amplitudes and EMG activity were seen in iTA and cMG during walking for the middle latency period (Table 1). For the static postures, only cTA did not show a significant correlation. Out of the five muscles that did show a significant correlation between reflex amplitude and EMG activity, iTA and cBF showed a negative correlation. Interestingly, the correlation values for the static condition are significantly higher (absolute mean = 0.74, $p < 0.05$) than those seen during walking (absolute mean = 0.55). The effects of different postures on the early and middle latency reflex amplitudes were also examined. Main effects for posture on the early latency reflex amplitude were observed for iBF, whereas iTA, iBF, and cBF showed a main effect on the middle latency reflex amplitude (not shown). The postures in which there was a modulation of reflex amplitude matched the postures in which there was a change in background EMG activity.

Table 1: Summary of linear regression analysis between latency reflexes and background EMG during standing and walking during SP nerve stimulation for the muscles of the lower limbs. Significant Pearson correlation coefficients (r) and indicated by asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$, NS no significant correlation).

Muscle	Task	Pearson r value early	Pearson r value middle	Muscle	Task	Pearson r value early	Pearson r value middle
iTA	static	NS	-0.93***	cTA	static	NS	NS
	walking	NS	-0.57***		walking	NS	NS
iMG	static	NS	0.52***	cMG	static	NS	0.77***
	walking	NS	NS		walking	NS	0.52***
iBF	static	NS	0.73***	cBF	static	NS	0.77***
	walking	NS	NS		walking	NS	NS

Lower limb kinematic responses during walking

Figure 7 shows the SP nerve stimulus-induced changes in joint angle through the step cycle for both ankles and both knees (ipsilateral on left-hand side of figure). During the stance-swing transition for each leg, a significant kinematic change occurred in both the ipsilateral and contralateral ankle, with an increased plantar flexion in the ipsilateral ankle (portions 9-10), and increased dorsiflexion in the contralateral ankle (portion 1). An increased flexion of the ipsilateral knee was also observed during stance (portion 13).

Upper limb responses

Subtracted EMG data for iPD and cPD for one subject during the step cycle with SP stimulation is shown in figure 5B. Modulation of cutaneous reflexes was also observed in the upper limbs during walking. Inhibition occurred during the stance portion (portions 5-8) of the step cycle for iPD, and also for the same portion of the step cycle (portions 14-16) in cPD, as highlighted by the light gray vertical box in the figure.

Except for a significant inhibition occurring during early stance in iAD, there were no significant early latency reflex responses in the muscles of the upper limbs across all subjects. The amplitude of the middle latency response in the upper limb muscles is shown in Figure 8, with the ipsilateral muscles on the left. A reciprocal crossed effect was noted between the ipsilateral and contralateral PD for the middle latency reflex period. A significant inhibitory

Figure 7: Stimulus-induced changes in joint angle (n=16 for ankle, n=5 for knee, means ± SEM) throughout the step cycle with SP nerve stimulation. Values are for the ipsilateral (left) and contralateral (right) ankle at the top, as well as the ipsilateral (left) and contralateral (right) knee at the bottom. Values have been normalized to the maximum range of motion for each subject, and are expressed as a percentage. Asterisks indicate effects significantly different from zero at $p < 0.05$. Arrows indicate dorsiflexion (DF) and plantar flexion (PF) for the ankle, as well as flexion (F) and extension (E) for the knee.

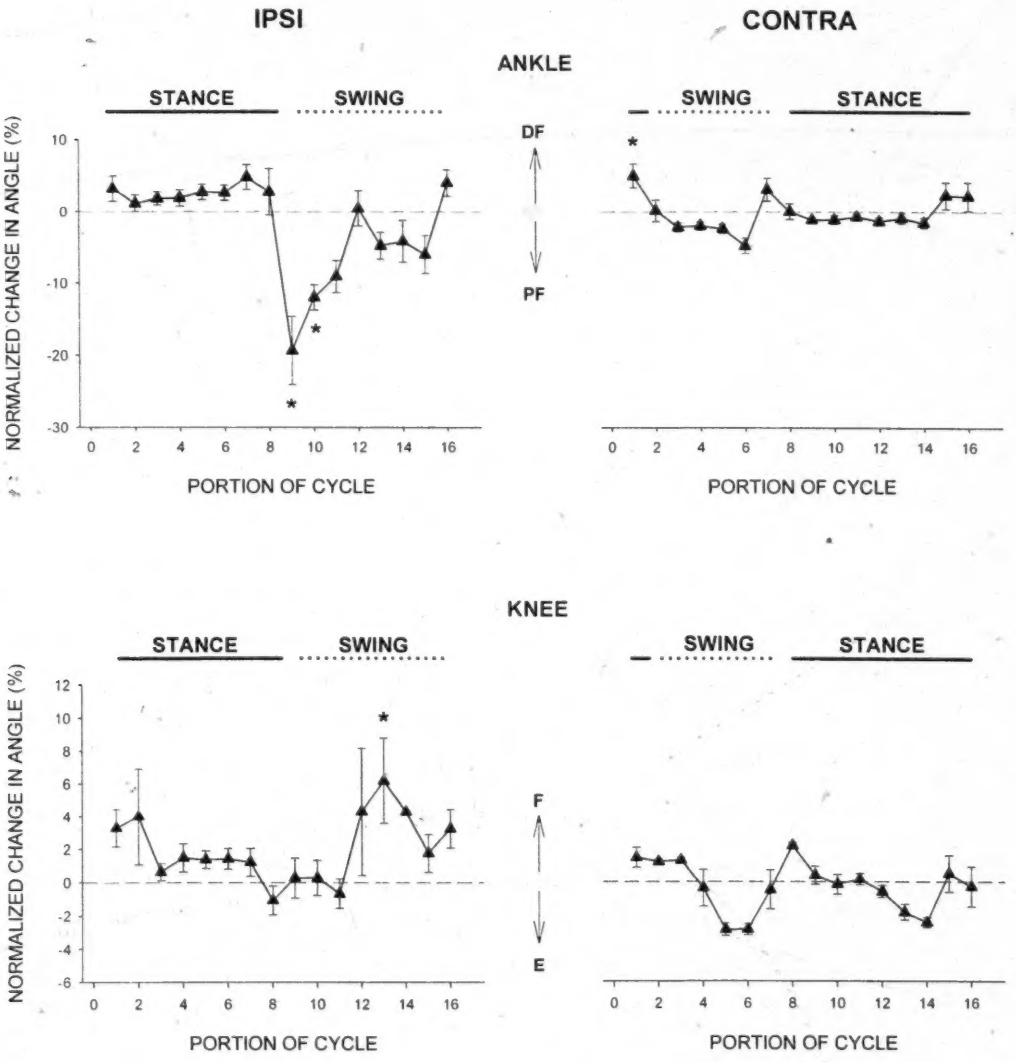
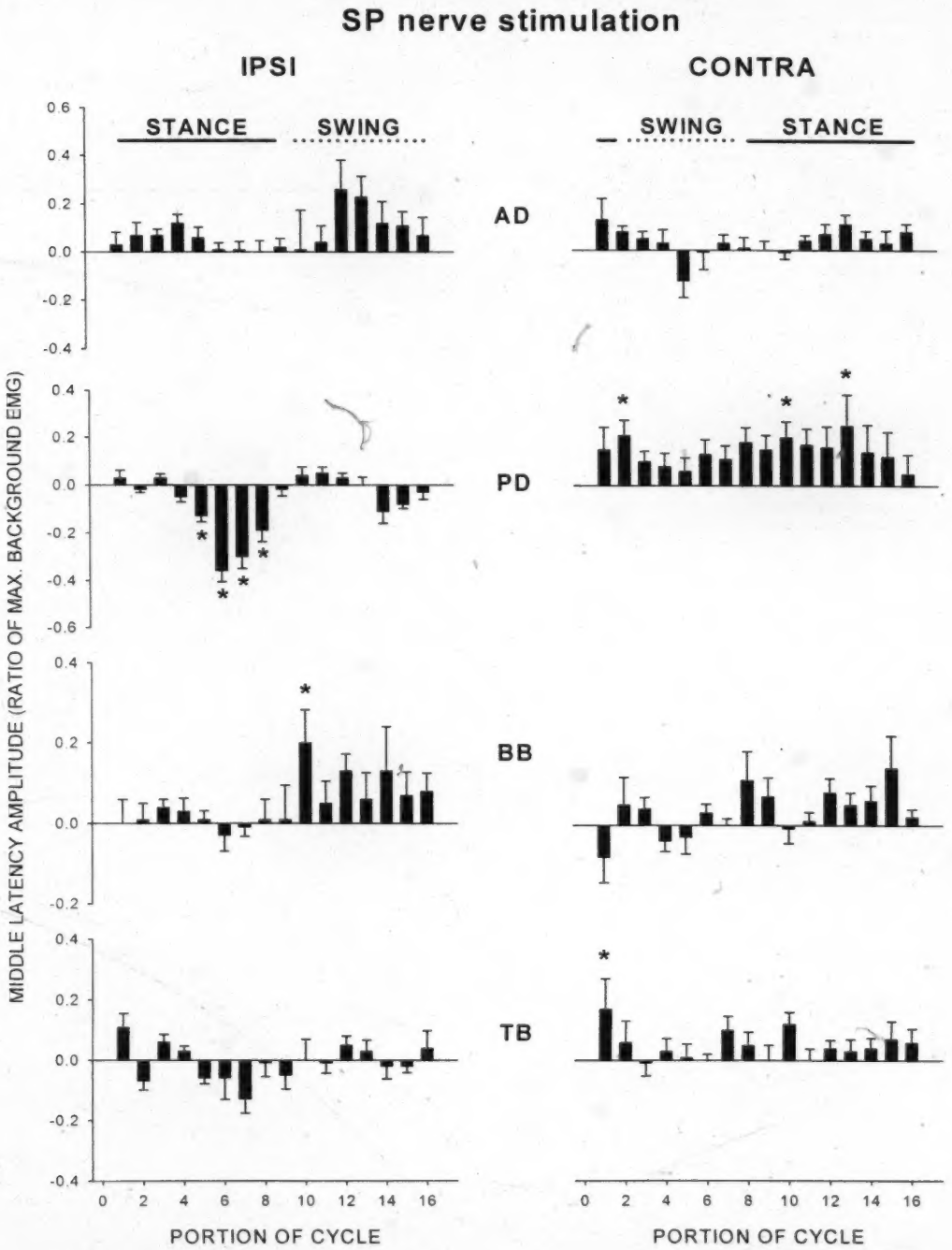


Figure 8: Middle latency (80-120 ms poststimulus) reflexes for muscles of the upper extremities averaged across all subjects (n=16, means ± SEM) for SP nerve stimulation throughout the step cycle. Reflex amplitudes have been normalized to the peak value of the background (unstimulated) EMG obtained in the step cycle for each subject, and are expressed as ratios. Asterisks indicate effects significantly different from zero at $p < 0.05$. Abbreviations are as in Figure 3.



response in iPD was seen during the latter portion of the stance phase (portions 5-8), while significant facilitation was seen in cPD also during stance (portion 10).

There was a significant net reflex response (facilitation) in cPD during early stance, the stance-swing transition, and during swing (not shown). It is interesting to note that facilitation was seen throughout the step cycle for cPD, whereas in iPD, inhibition occurred during the stance-swing transition as well as during stance.

Task-dependency of SP nerve cutaneous reflexes in the upper limbs

Table 2 shows the early and middle latency cutaneous reflex amplitudes plotted against background EMG across the step cycle and for the static postures. This is done to determine whether the reflexes were scaled according to the level of background EMG. No significant correlations were observed during the early latency time period for any of the upper limb muscles while in the static postures and during walking.

A significant negative correlation between middle latency reflex amplitudes and EMG activity was seen in only iPD during walking. For the static postures, only iAD and iPD did not show a significant correlation. Both elbow flexors, as well as cTB showed a positive correlation, while iTB, cAD, and cPD showed negative correlations. As with the lower limb muscles, the correlation values for the static conditions were significantly higher (absolute mean = 0.64, $p < 0.05$) than those for walking (absolute mean = 0.50).

Table 2: Summary of linear regression analysis between latency reflexes and background EMG during standing and walking during SP nerve stimulation for the muscles of the upper limbs. Significant Pearson correlation coefficients (r) and indicated by asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$, NS no significant correlation).

Muscle	Task	Pearson r value early	Pearson r value middle	Muscle	Task	Pearson r value early	Pearson r value middle
iAD	static	NS	NS	cAD	static	NS	-0.96***
	walking	NS	NS		walking	NS	NS
iPD	static	NS	NS	cPD	static	NS	-0.69**
	walking	NS	-0.50***		walking	NS	NS
iBB	static	NS	0.70***	cBB	static	NS	0.64**
	walking	NS	NS		walking	NS	NS
iTB	static	NS	-0.59**	cTB	static	NS	0.88**
	walking	NS	NS		walking	NS	NS

Upper limb kinematic responses during walking

No significant kinematic change occurred in either the ipsilateral or contralateral elbow or shoulder as a result of SP nerve stimulation.

Responses to SR nerve stimulation during locomotion

Lower limb responses

Single subject subtracted EMG data across the step cycle with SR nerve stimulation is shown in Figure 9A. Cutaneous reflexes were modulated in the muscles of the lower limbs, according to the portion of the step cycle in which the stimulation occurred. Inhibition was apparent in iMG and cMG during stance for both the ipsilateral (portions 5-7) and contralateral (portions 11-16) sides respectively, as depicted by the light gray vertical boxes in the figure.

In all six lower limb muscles that were recorded, only one significant reflex response was observed at the early latency reflex period. Contralateral TA displayed inhibition during late stance (not shown). For the middle latency reflex period, shown in Figure 10 (ipsilateral in the left column), inhibition was observed during swing for both iTA (portion 15) and cTA (portions 7-8). A significant inhibitory response was also observed in iMG and cMG during stance (portion 6 and portions 13-14 respectively). Ipsilateral BF did not display any significant middle latency reflex responses, while in cBF, a significant inhibition was observed in the late portion of the stance phase (portion 1). Notice that the reflex

Figure 9: Subtracted EMG traces from one subject evoked by SR nerve stimulation during the step cycle. Top two traces are from iMG (left) and cMG (right) (A), while the bottom two traces are from iPD (left) and cPD (right) (B). The grey rectangle highlights the response observed during particular portions of the step cycle (portions indicated by the numbers to the right of each graph; 1 indicates ipsilateral heel strike). Note the similarity in sign of the reflex response between iMG and cMG (suppression) during the stance phase, compared to the reflex reversal in sign observed in cMG with SP nerve stimulation (facilitation, Fig. 4A). Facilitation is seen in iPD, which is opposite to that observed in the same muscle during SP nerve stimulation (suppression, Fig. 4B). As well, the facilitation is observed throughout the step cycle, whereas suppression was only seen during stance with SP stimulation. Stimulus artifact has been removed from each trace, and replaced by a black vertical bar extending from time 0 out to approximately 30 ms poststimulus. Abbreviations are as in Figure 3.

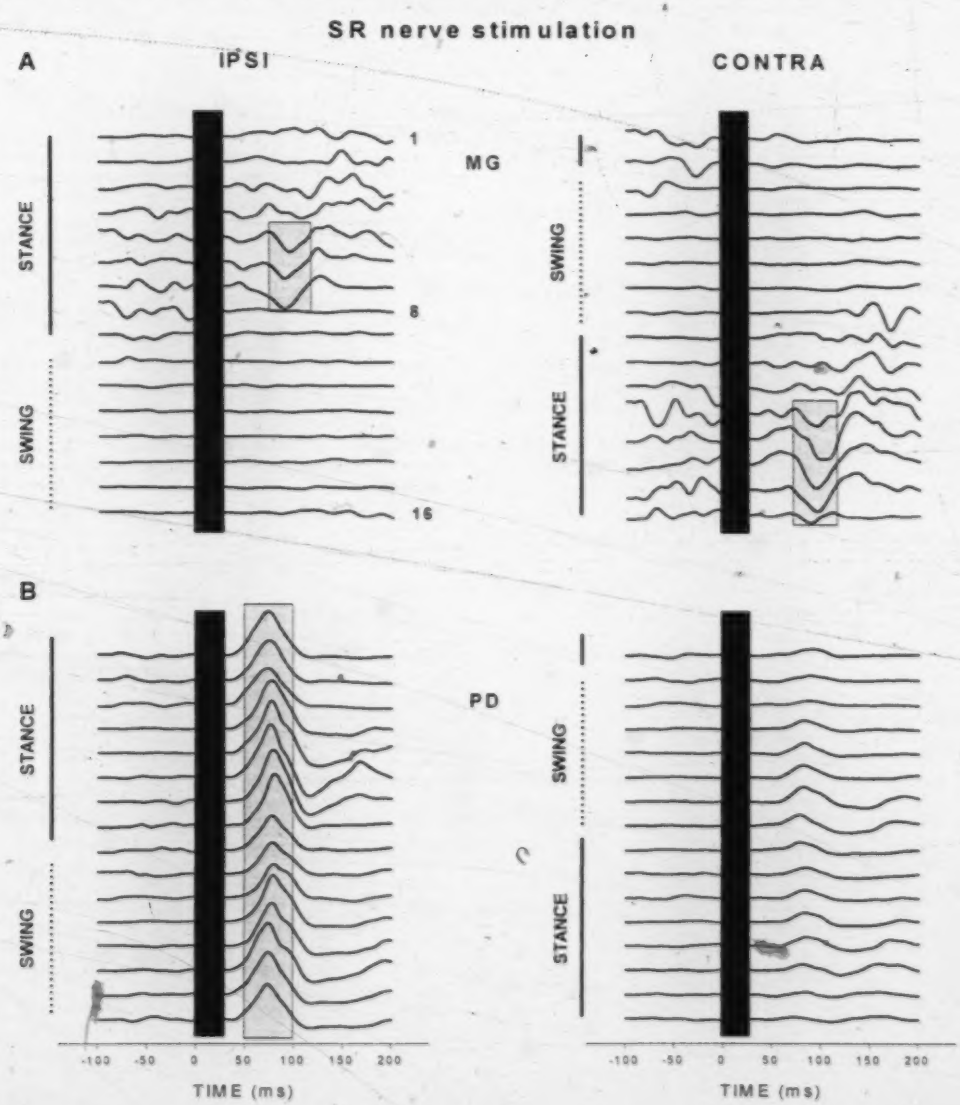
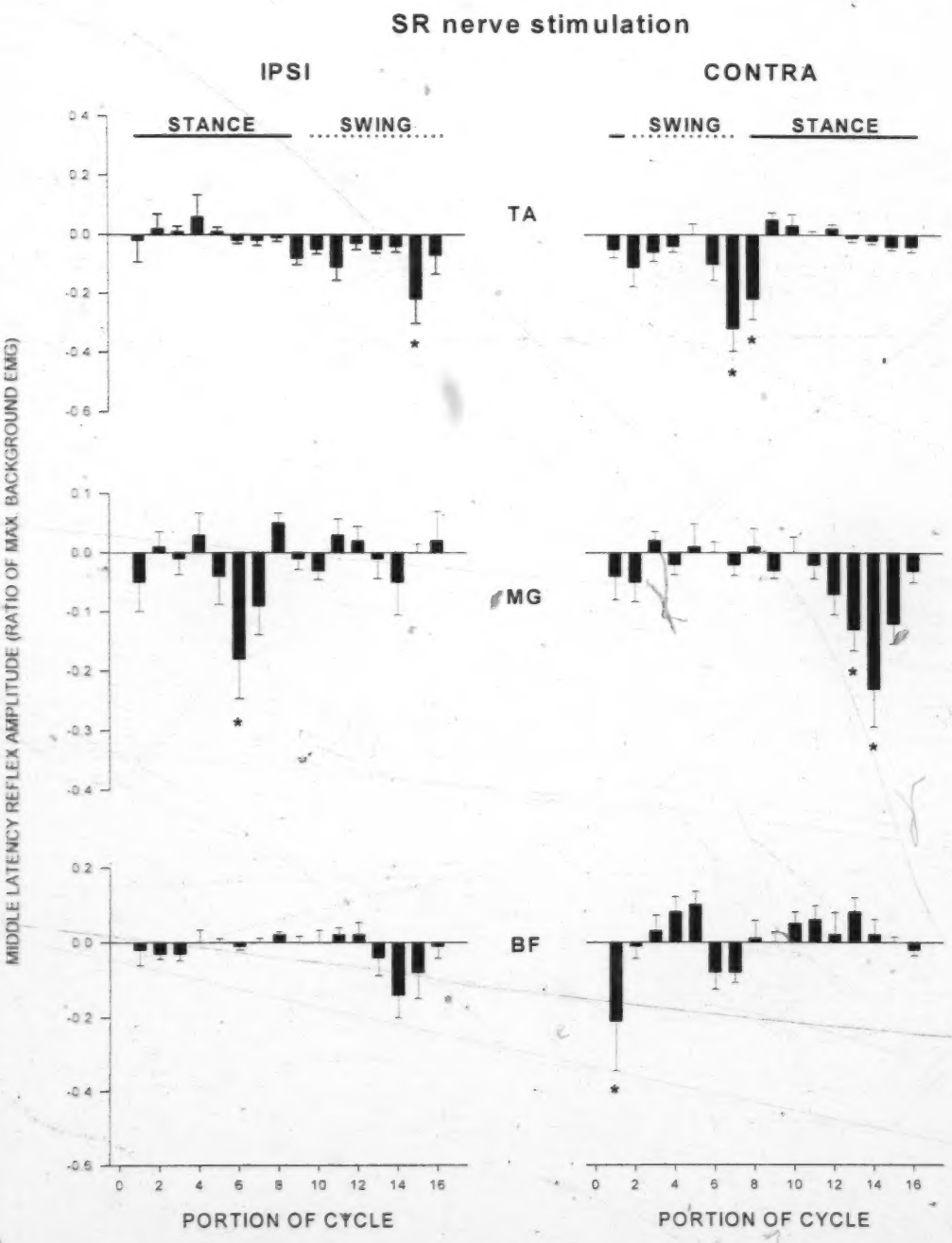


Figure 10: Middle latency (80-120 ms poststimulus) reflexes for muscles of the lower extremities averaged across all subjects (n=15, means ± SEM) for SR nerve stimulation throughout the step cycle. Reflex amplitudes have been normalized to the peak value of the background (unstimulated) EMG obtained in the step cycle for each subject, and are expressed as ratios. Asterisks indicate effects significantly different from zero at $p < 0.05$. Abbreviations are as in Figure 3.



sign was the same across the body for the same part of the step cycle in both TA and MG. Significant inhibition was observed in iTA and cTA during swing. Inhibition was also observed in iMG and cMG, however, the inhibition occurred during the stance portion of the cycle.

There was a significant net reflex response in iMG, which showed facilitation during stance (not shown). This is an interesting finding, as this goes against the inhibition observed in the middle latency period for iMG. However, this is probably due to the $ACRE_{150}$ being not as sensitive to minor fluctuations at a given latency (i.e. the middle latency response) (Zehr et al., 1998).

Task-dependency of SR nerve cutaneous reflexes in the lower limbs

Significant correlations between background EMG level and cutaneous reflex amplitude were only observed during the static postures in the lower limb muscles with SR nerve stimulation (not shown). There were only two significant correlations. For the early latency period, a significant correlation of 0.96 ($p < 0.05$) was observed in iTA during the static postures.

For the middle latency period, a significant correlation of –0.75 ($p < 0.0001$) between reflex amplitude and background EMG activity was seen for cBF during the static postures. It is important to note that the EMG levels during static contraction for the lower limb muscles were similar to that seen during walking.

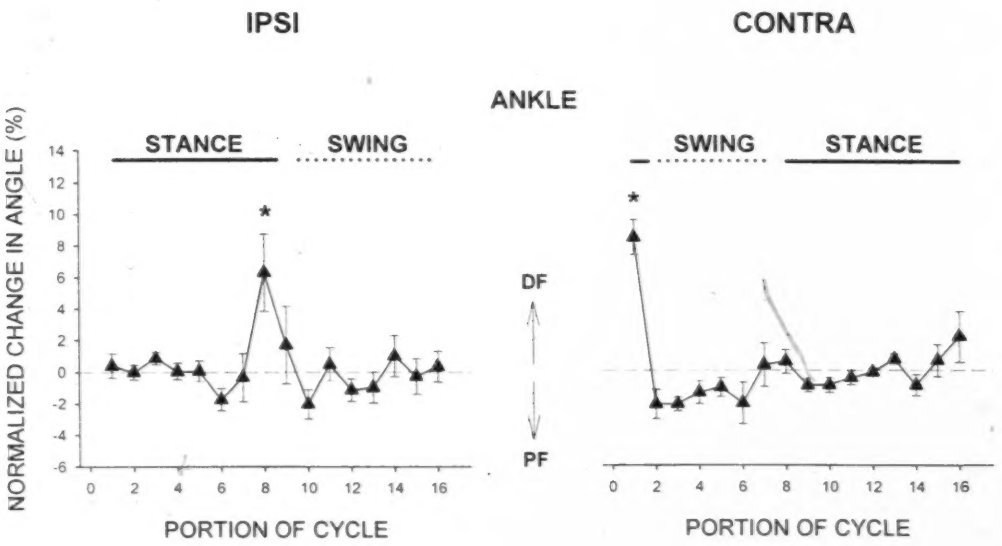
A main effect for posture on the middle latency reflex amplitudes was observed for iTA and cBF (not shown). However, as was observed with SP nerve

stimulation, the cases in which there was a significant difference between postures with respect to reflex amplitude coincided with the cases that showed changes in the background EMG activity.

Lower limb kinematic responses during walking

The kinematic responses for the ipsilateral and contralateral ankles with SR nerve stimulation are shown in Figure 11. A significant kinematic change was observed for both the ipsilateral and contralateral ankle during the stance-swing transition, with an increased dorsiflexion in both the ipsilateral (portion 8) and contralateral ankle (portion 1). There was no significant correlation between the changes in ankle or knee angle and the net reflex response for the muscles around each joint for either side of the body after SR nerve stimulation.

Figure 11: Stimulus-induced changes in joint angle (n=15, means ± SEM) throughout the step cycle with SR nerve stimulation. Values are for the ipsilateral (left) and contralateral (right) ankle. Values have been normalized to the maximum range of motion for each subject, and are expressed as a percentage. Asterisks indicate effects significantly different from zero at $p < 0.05$. Arrows indicate dorsiflexion (DF) and plantar flexion (PF).



CHAPTER 5 - Discussion

This study represents the first effort to investigate cutaneous interlimb reflexes from SP and SR stimulation in both the lower and upper extremities during walking. The major finding of this study is that cutaneous interlimb reflexes are phase-modulated during the walking cycle. Reciprocal organization and coordination of reflexes (i.e. between the ipsilateral and contralateral sides of the body, facilitation and inhibition), as well as pathways mediating these reflexes are discussed. The kinematic outcomes, as well as the functional interpretation of these responses are also discussed.

EMG patterns in arm and leg muscles during walking

As seen in Figures 3 and 4, the level of modulation, as measured by the modulation index (MI) was generally greater in the muscles of the lower extremities during walking. MI values were in the range of 76.37% to 84.5% in the muscles of the lower extremities, versus a range of 37.83% to 75.27% in the arm muscles. Reciprocal activity was observed across the body for the muscles of the legs. Phasic reciprocal muscle activity was observed between flexor and extensor muscles at both the ipsilateral (iTA/iMG) and contralateral (cTA/cMG) ankles. However, except for PD, the MI values for the muscles of the upper extremities were much lower than that observed for the muscles of the lower extremities. Reciprocal and phasic activity patterns were observed between the flexor and extensor muscles at the shoulders (iAD/iPD, cAD/cPD), while reciprocal activity was observed at the elbows (iBB/iTB, cBB/cTB). The activity of

the elbow flexors and extensors appeared to be similar to each other. Additionally, even though exhibiting a rhythmic pattern of activation, the EMG activity for PD was different from that observed in arm cycling (Zehr & Kido, 2001). MI values during arm cycling were lower than those observed in this study during walking by approximately 15% and 18% for iPD and cPD respectively. The other arm muscles displayed higher MI values than those seen during arm cycling, with the biggest difference in AD, with MI values being higher in arm cycling by 37.2% and 28.5% for iAD and cPD respectively.

The temporal similarity in EMG activity between BB and TB is probably due to cocontraction of these two muscles throughout the movement cycle. This could serve to control elbow movement due to momentum of the shoulder during arm swing. The large difference in average MI values between AD and PD (50.18% and 72.43% respectively) is also hard to explain, as one would expect similar MI values between antagonistic muscles that are being rhythmically activated. However, it would be expected that the MI values would be generally higher during arm cycling than in walking, due to the greater range in motion occurring at the shoulder and the elbow.

Interlimb cutaneous reflexes arising from different nerves during walking:

SP stimulation

Middle latency reflexes in all lower limb muscles (Fig. 6) showed modulation according to which part of the step cycle in which SP nerve stimulation occurred (i.e. phase-modulation). In TA, a significant inhibition was

noted during late swing for both the ipsilateral and contralateral sides. However, a reciprocal crossed effect was noted across the body for MG and BF. In the stance phase, a significant inhibition was observed for iMG, but cMG displayed a significant facilitation. For iBF, significant facilitation was seen during swing, while inhibition was observed in cBF during the same part of the step cycle. In the upper limbs, a reciprocal crossed effect was also observed in PD during SP nerve stimulation (Fig. 8). Significant inhibition was seen in iPD during stance while significant facilitation was seen in cPD during the same part of the step cycle. This reciprocal crossed effect occurred in the same part of the step cycle for the respective leg. Interestingly, this gating of these crossed responses was also noted in other studies (Duysens et al., 1990a, b). These studies stated that the responses observed were dependent on the phase of the leg in which the response occurred, and not on the phase of the stimulated leg.

SR stimulation

Compared to the responses observed during SP nerve stimulation, the responses in the muscles of the lower extremities are similar during SR nerve stimulation (Fig. 10). Inhibition was observed in iTA and cTA during late swing, consistent with SP nerve stimulation. However, a reversal in sign was observed in cMG between the two different nerve stimulation protocols. During SR stimulation, significant inhibition was seen in cMG during stance. With SP stimulation however, facilitation was seen in the same muscle during the same part of the step cycle. This finding is an example of nerve specificity, a feature that has been shown before in the muscles of the lower limb during human

walking (Van Wezel et al., 1997; Zehr et al., 1997), and for the muscles of the upper limbs during arm cycling (Zehr & Kido, 2001).

The responses to SR nerve stimulation in the muscles of the upper extremities (Appendix A) were shown to display phase-modulation. That is, the amplitude of the reflexes is dependent upon the phase of the step cycle in which they occurred. There was no apparent reciprocal coordination of reflexes between the ipsilateral and contralateral sides of the body (Figure 2, Appendix A). For instance, in both iPD and cPD, the middle latency response was typically excitatory. This is in contrast to the middle latency response in iPD seen with SP nerve stimulation, which showed significant inhibitory responses during stance (Figure 8). The pattern of reflex modulation seen with SR nerve stimulation was more similar to that observed during arm cycling with the same nerve being stimulated (Zehr & Kido, 2001).

Pathways mediating the responses observed

This difference in responses associated with the specific nerve being stimulated suggests that both the SP and SR nerves project to the ankle extensor on the contralateral side via different parallel pathways. Specifically, cMG might receive projections from the SR nerve that have gone through inhibitory interneurons in the spinal cord. In contrast, projections from the SP nerve may not have gone through this type of interneuron. That is, the final projection onto cMG from the SP nerve is via a different pathway compared to the SR nerve. The same type of pathway may also be responsible for the

difference in response in iPD between the two nerve stimulation protocols. It is also suggested that a convergent pathway may be mediating the responses from both the SP and SR nerves onto the muscles of the lower extremities on the ipsilateral side. This would explain the similar responses seen in iTA and iMG during both SP and SR nerve stimulation.

It has been suggested that a propriospinal pathway governs the transmission of interlimb reflexes (Zehr et al., 2001a). The evidence for this was the early latency values noted for these responses during static muscle contractions. The early latency component of the interlimb reflexes observed was generally shorter than 70 ms. This was suggested by Nielsen et al. (1997) as the earliest possible latency for a transcortical effect. However in the present study, the majority of reflexes were observed in the middle latency window. This suggests that the early latency interlimb reflexes may be suppressed during locomotion.

The reflexes observed during walking may be mediated by transcortical pathways, which would extend the latency value. The suggestion has been made that transcortical pathways may play a role in non-early latency reflexes (Christensen et al., 2000). Also supporting this idea are findings by Quintern et al. (1985), in which responses in the arm of neurologically intact subjects were evoked by step increases in treadmill speed during walking. The authors noted a strong relationship between the arm responses and cerebral potentials that were recorded at the time of the disturbances, and suggested the responses originated

from transcortical areas. This suggests that in neurologically intact humans, supraspinal centres contribute to interlimb reflexes.

Task-dependency of interlimb reflexes

By examining the correlation between the reflex amplitudes and the background EMG levels at the moment that the reflexes were collected, it was possible to show if the size of the reflex was associated with the level of ongoing muscle activity. In the present study, 42% of the possible correlations between early and middle latency reflex amplitudes and the background EMG of the muscles of the lower extremities with SP stimulation during the static conditions were significant (Table 1), as compared to 17% during walking. The discrepancy in the occurrences of significant correlations between conditions is maintained when looking at the reflexes evoked in the muscles of the upper extremities during walking under the same nerve stimulation protocol. During the static postures, 38% of the correlations were significant, while 6% were significant during walking (Table 2). For SR nerve stimulation, there was no difference in the percentage of significant correlations between the static postures and walking (8%) for the muscles of the lower extremities. However for the muscles in the arms, 75% of correlations between early and middle latency reflex amplitudes and background EMG were significant during the static postures, and none during walking with SR nerve stimulation (Table 1, Appendix A). In addition, the correlation values were significantly higher ($p < 0.05$) during the static conditions versus those values seen during walking for the lower extremities, as well as for

the upper extremities during SP stimulation. A lack of correlation between reflex amplitude and background EMG means that the amplitude of the reflex observed was not directly related to the EMG activity.

Komiyama et al. (2000) also found that reflexes evoked during standing correlated with background EMG, but during walking, this correlation was lost. The authors had the subjects perform static contractions mimicking heel strike and late stance in an attempt to match the EMG levels during walking. While matching static postures to walking, the assumption can be made that limb loading and the sensory feedback from muscle stretch are similar between tasks. If this is the case, then the difference in correlations between background EMG and reflex amplitude for the static postures and during walking could be due to some central output (Zehr et al., 2001b). The results suggest the task-dependent cutaneous reflexes observed in the muscles of the lower and upper extremities during walking, in contrast to the static postures, may be controlled by segmental CPGs acting at the legs (Komiyama et al., 2000, Zehr et al., 2001b) and arms (Zehr & Kido, 2001). The modulation of the reflexes observed during the walking cycle also corroborates the idea of CPGs controlling the gating of the cutaneous reflexes (Duysens & Van de Crommert, 1998).

Taken together, these results provide partial evidence for the role of segmental CPGs (i.e. at the cervical and lumbar levels) acting at the arms and legs respectively during walking, with respect to reflex modulation. Additionally, the reflexes observed in upper and lower extremity muscles on both the ipsilateral and contralateral sides of the body at the same portion of the step

cycle suggests that a segmental CPG may be the mechanism allowing for the control of the cutaneous reflexes observed. Evidence for segmental, as opposed to supraspinal control of reflexes, is given by experiments showing the presence of phase-dependent modulation of reflexes in chronic spinal cats during treadmill walking (Forssberg et al., 1975, 1976, 1977, 1979).

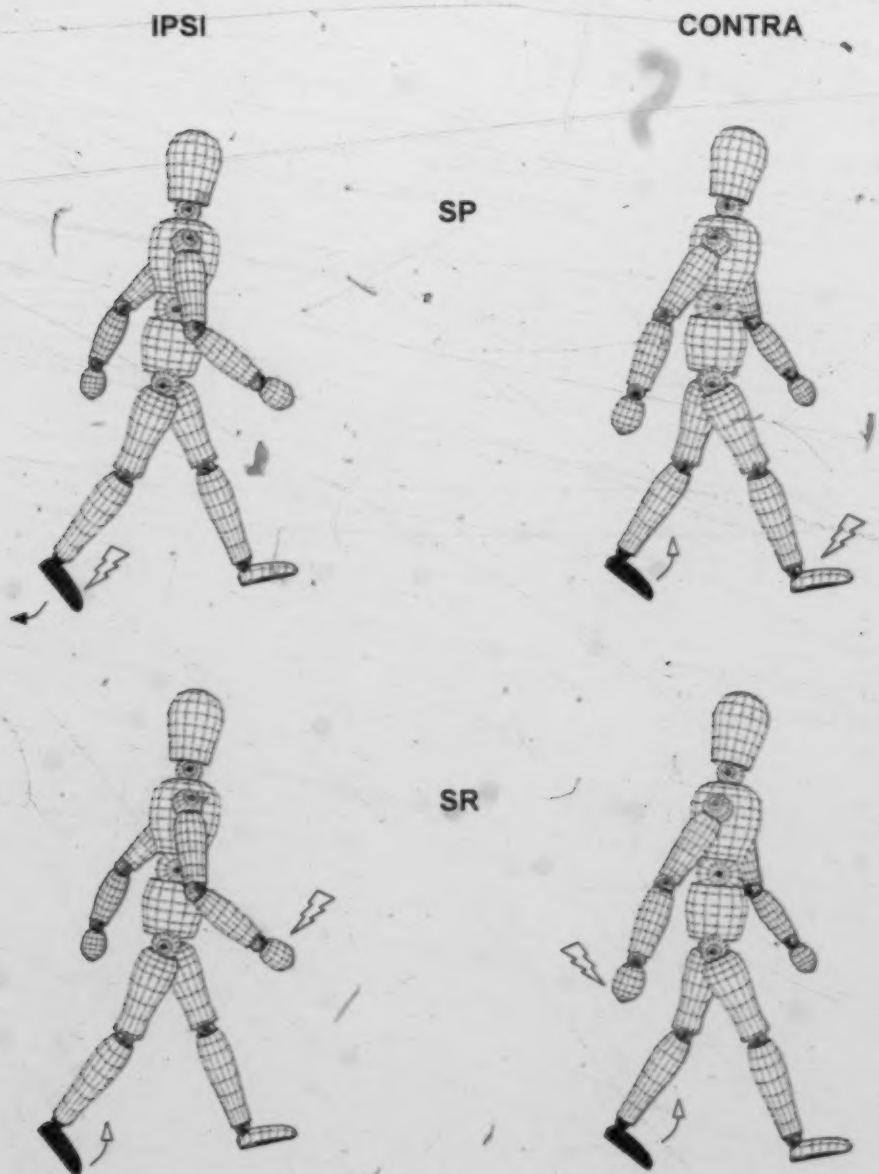
Kinematic outcomes and functional relevance

The kinematic changes observed at the ankle during SP and SR nerve stimulation are summarized in Figure 12. The figure shows an opposite response in the ipsilateral ankle to SP (plantar flexion) and SR (dorsiflexion) nerve stimulation. In contrast, the contralateral ankle showed the same response to both SP and SR stimulation (dorsiflexion).

The responses in the ipsilateral leg muscles with SP nerve stimulation were similar to those found in previous studies, with suppression in iTA and iMG during late swing and midstance respectively (Van Wezel et al., 1997; Zehr et al., 1997). There was also a significant facilitation in iBF, in agreement with findings by Zehr et al. (1997). Additionally, an increase in plantar flexion was also observed during the stance-swing transition for the ipsilateral ankle (Fig. 7, top left), and an increase in ipsilateral knee flexion was noted during swing (Fig. 7, bottom).

Altogether, the responses in the ipsilateral lower leg with SP nerve stimulation are typical of a stumbling corrective response, which was also found in humans during walking by Zehr et al. (1997). As first described by Forssberg

Figure 12: Summary of the kinematic change at the ankle with SP (top) and SR (bottom) nerve stimulation at the stance-swing transition for both the ipsilateral (left) and contralateral (right) sides. Solid foot represents the foot in which the response to stimulus occurred. ⚡ indicates site of stimulation; solid arrow indicates plantar flexion; open arrow indicates dorsiflexion.



(1979) in intact cats, the stumbling corrective response consists of a change in limb trajectory during swing in response to an electrical or mechanical perturbation to the dorsal surface of the distal hindlimb. This response consisted of an increase in knee, hip, and ankle flexion, which together, would allow the cat to continue the forward progression of the swing limb with minimal disturbance to gait. In the human, this stumble corrective response is slightly different in that there is reduced flexion (dorsiflexion) of the ankle. This would potentially allow the foot to be dragged over an obstacle during swing, thereby allowing for the continuation of forward gait, rather than hitting the obstacle, which could occur if there was an increase in dorsiflexion. This finding has also been observed in studies focusing on the control strategies that humans utilize when recovering from a trip during walking (Eng et al., 1994; Rietdyk & Patla, 1998). These studies showed that subjects, in response to a perturbation applied to the leg during early swing, showed an "elevating strategy" of the swing limb to step over the perturbation. This behaviour is similar to the stumble-corrective response observed in the present study.

In examining the contralateral leg muscles, the responses with SP nerve stimulation were similar to that found by Van Wezel et al. (1997), with cTA and cBF showing a significant inhibition during swing (Fig. 6). In cMG (a muscle not recorded from by the aforementioned authors), significant facilitation was observed in the stance portion of the step cycle. A kinematic change in the contralateral ankle near the stance-swing transition was noted during SP nerve stimulation, with an increase in dorsiflexion (Fig. 7, top right). This response is

opposite to that seen in the ipsilateral ankle during the same portion of the step cycle.

It is difficult to interpret the responses in the contralateral leg in a functional manner. A facilitation response in cMG during stance (i.e. ipsilateral leg is in swing) during SP nerve stimulation might be able assist a stumbling corrective response, which is seen in the ipsilateral leg. This facilitation could assist toe-off of the contralateral foot in response to an obstacle encountered by the ipsilateral foot. Combined with the ipsilateral stumbling corrective response, this could allow for the ipsilateral leg to be moved through the swing phase of the step cycle quicker than normal, thus allowing for it to contact the ground sooner to regain a more stable base of balance. The inhibitory response in cBF during the latter portion of swing (i.e. as the contralateral leg is swinging forward) is also hard to interpret, but this response may allow for the knee to be extended easily, thus allowing the foot to quickly contact the ground. However, there were no significant kinematic responses for the contralateral knee to corroborate this hypothesis. The increase in dorsiflexion in the contralateral ankle near the stance-swing transition could be interpreted as a stumble-avoidance response. This response would retard the forward progression of gait by making contralateral toe-off (i.e. plantar flexion) more difficult.

During SR nerve stimulation, TA also showed an inhibitory response at the same portions of the step cycle as with SP nerve stimulation. The inhibitory response during stance during SP stimulation was also observed with SR nerve stimulation. However, there was a reversal in the sign of the reflex between

nerves for cMG. SP nerve stimulation produced a facilitatory response during stance, which reversed to inhibition during the same portion of the step cycle with stimulation of the SR nerve. Observing the kinematic response during SR nerve stimulation, there was an increase in dorsiflexion for both ankles, when they were each at the stance-swing transition of the step cycle.

At the stance-swing transition, the hand is positioned forward away from the torso, while the foot is ready to enter the swing phase. In this position, the innervation area of the SR nerve (dorsolateral portion of the hand) is in an ideal location to contact an obstacle during walking. If the hand were to hit an object while in front of the body, an increase in dorsiflexion of the ankle near the stance-swing transition could help prevent forward progression by acting against toe-off, as also seen in the ipsilateral ankle during SP nerve stimulation. This in turn could serve to help stop forward locomotion, thereby preventing the body from colliding with an object. Thus, as suggested by Zehr and Stein (1999), reflexes can be utilized to alter limb mechanics in a functional manner during walking.

In studying the results, it is interesting to note that there is no apparent correlation between the net reflex response ($ACRE_{150}$) and the kinematic change in ankle angle during both nerve stimulation protocols. That is, there seems to be no apparent explanation for the mechanical changes in joint angle. One possible reason for this discrepancy could be due to other muscles in the lower leg accounting for the change in joint angle (e.g. soleus, lateral gastrocnemius) that were not recorded. Another possibility is that minor non-statistically significant changes in muscle activity may have summed to cause a change in joint angle.

CHAPTER 6 - Conclusion

The present study investigated the nature of interlimb cutaneous reflexes during walking. Interlimb reflexes were shown to be reciprocally organized and coordinated during walking. Specifically, the reflexes observed at the muscles differed in sign according to the nerve being stimulated as well as the side on which the muscle was with respect to the site of stimulation. This finding provided evidence for the existence of parallel and convergent pathways mediating the responses between the upper and lower extremities. Additionally, significant kinematic changes were observed at the ankles during walking with nerve stimulation. This may serve to assist in a stumble corrective / stumble avoidance response, in which the response is specific to the nerve being stimulated.

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APPENDIX A

Modulation of cutaneous reflexes in arm muscles during walking: further evidence of similar control mechanisms for rhythmic human arm and leg movements*

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Running head: cutaneous reflexes in arm muscles during walking

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Abstract

Stimulation of cutaneous nerves innervating the hand evokes prominent reflexes in many arm muscles during constrained arm cycling. We hypothesized that the mechanisms controlling reflex modulation during the rhythmic arm swing of walking would be similar to that documented during arm cycling. Thus, we expected cutaneous reflexes to be modulated by position in the walking cycle (phase-dependence) and be different when walking compared to contraction while standing (task-dependence). Subjects performed static postures similar to those occurring during walking, and also walked on a treadmill while the superficial radial nerve was electrically stimulated pseudorandomly throughout the step cycle. EMG was recorded bilaterally from upper limb muscles and kinematic recordings were obtained from the elbow and shoulder joints. Step cycle information was obtained from force-sensing insoles. Analysis was conducted after averaging contingent upon the occurrence of stimulation in the step cycle. Phase-dependent modulation of cutaneous reflexes at early (~50-80 ms) and middle (~80-120 ms) latencies was observed. Coordinated bilateral reflexes were seen in posterior deltoid and triceps brachii muscles. Task-dependency was seen in that reflex amplitude was only correlated with background EMG during static contraction (75% of comparisons for both early and middle latency reflexes). During walking, no significant relationship between reflex amplitude and background EMG level was found. The results show that cutaneous reflex modulation during rhythmic upper limb movement is similar to that seen during arm cycling and to that observed in leg muscles during

locomotion. These results add to the growing body of evidence suggesting that, during cyclical movements of the arms and legs, similar neural mechanisms are operating during movement (e.g. central pattern generators) control reflex output.

KEY WORDS: movement control, reflex, hand, arm, central rhythm generator, afferent feedback

Introduction

Some time ago, Elftman (1939) proposed that the rhythmic arm motion associated with human walking was not an example of pure pendular movement. Instead, it was suggested that active muscle forces were required to generate rhythmic arm swing. Later, electromyographic recordings corroborated this conclusion (Fernandez-Ballesteros et al., 1965). It was shown that during walking there is rhythmic movement of the upper limbs involving active contraction of upper limb muscles (particularly extensors) in concert with lower limb movement (Hogue, 1969). The function of arm swing has been suggested to allow for smooth, non-jerky motion during locomotion (Jackson et al., 1983). Furthermore, the idea has been put forward that arm movement during walking is controlled by spinal central pattern generators (CPGs) acting to control rhythmic arm movement during walking (Jackson, 1983; Jackson et al., 1978, 1983). However, this proposal has primarily remained a theoretical argument and has received little experimental attention.

Cutaneous reflexes are extensively modulated by position within a movement (phase-dependent) and between motor tasks (task-dependent; for review see Brooke et al., 1997). During a static contraction, reflex amplitude typically increases with EMG level (so-called "automatic gain compensation"; Matthews, 1986). However, there is considerable documentation that cutaneous reflex amplitude may be independent of EMG level during rhythmic movements such as running (Duysens et al., 1993), walking (Komiyama et al., 2000), leg cycling (Brooke et al., 1999; Brown & Kukulka, 1993; Zehr et al., 2001), and arm

cycling (Zehr & Kido, 2001). The phase- and task-modulation of cutaneous reflexes during rhythmic movement has been suggested to infer activity of a CPG (Duysens & Tax, 1994; Zehr et al., 2001). Activity of a CPG could explain observations of phase- and task-dependency via premotoneuronal gating of afferent feedback (Duysens & Tax, 1994).

To date, there has been very little study of cutaneous reflex modulation in arm muscles during the natural and unconstrained motor task of rhythmic arm swing during walking. Dietz et al. (2001) recently described modulation of cutaneous reflexes in arm muscles during walking evoked by stimulation of the distal tibial nerve at the ankle. It was suggested that activity of a CPG could underlie this control and might be a vestigial holdover from quadrupedal ancestry (Dietz, 2002). However, the modulation of reflexes in the arms could presumably have been affected by the gating of transmission from tibial nerve afferents in the lumbar cord.

The purpose of this study was to evaluate cutaneous reflex modulation in arm muscles during walking evoked by stimulating a nerve innervating the hand. If phase- and task-dependency is observed, this would support the hypothesis that rhythmic arm movements are controlled by similar neural mechanisms. This would also indirectly corroborate the assertion of Jackson (1983) and Dietz (2002; Dietz et al., 2001; Wannier et al., 2001) that the arm swing of locomotion may be, at least in part, controlled by a CPG. A portion of this work has appeared in abstract form (Zehr & Haridas, 2001).

Methods

Subjects

Fifteen subjects ranging in age from 18 to 34 years and who were free from documented neurological disease participated in the experiments with informed, written consent. The project was conducted under the sanction of the Human Research Ethics Board (Panel B) at the University of Alberta and performed according to the Declaration of Helsinki.

Protocol

The general experimental methodology and protocol are similar to that described in previous experiments involving cutaneous reflex modulation during walking (Zehr et al., 1997) and arm cycling (Zehr & Chua, 2000; Zehr & Kido, 2001) and therefore only differences in methodology are highlighted here. Subjects performed two main tasks: 1) treadmill walking with natural arm swing; and 2) five static postures in which the arms were held in positions mimicking those observed at different points in the step cycle (Komiyama et al., 2000). Cutaneous reflexes were evoked during both tasks by stimulating the superficial radial (SR; innervates dorsolateral portion of hand) nerve at the wrist.

Nerve stimulation

Nerve stimulation was pseudorandomly delivered approximately once every 3 steps during movement and approximately once every second during static contraction with a Grass S88 (Grass Instruments, AstroMed Inc.) stimulator

connected in series with an SIU5 isolator and a CCU1 constant current unit. The SR nerve was stimulated at 2-3 x the threshold for radiating paresthesia with a train of 5 x 1.0 ms pulses at 300 Hz applied through bipolar surface electrodes placed just proximal to the radial head on the right arm. Appropriate stimulation location was checked by determining that radiating paresthesia was evoked into the cutaneous field of the SR nerve (dorsolateral portion of the right hand).

Electromyography (EMG)

Bilateral recordings were made from biceps (BB) and triceps (TB) brachii, and anterior (AD) and posterior (PD) deltoid muscles. EMG signals were pre-amplified and bandpass filtered at 100-300 Hz (P511 Grass Instruments, AstroMed, Inc.).

Kinematics and step cycle timing

In some subjects (numbers are given in parentheses), kinematic recordings were obtained from elbow (ipsilateral n=11, contralateral n=10) and shoulder (ipsilateral n=4, contralateral n=5) joints using lightweight goniometers (Biometrics, Inc.). Step cycle information (e.g. related to heel contact) were obtained from force-sensitive resistors placed into the insoles of subjects shoes (see Zehr et al., 1997; Zehr et al., 1998).

Data acquisition and analysis

Data were acquired at a sampling rate of 1000 Hz with a 12 bit A/D converter connected to a computer running custom-written (Dr. Romeo Chua, University of British Columbia) LabView (National Instruments, Austin TX) virtual instruments. For the walking trials, offline analysis was conducted to divide the step cycle into 16 separate bins, beginning with right heel contact. Stimuli were then aligned to delivery within each step cycle bin and averaged together. Control data obtained from steps without stimulation were used to create subtracted traces (~10-20 observations per bin) of reflex EMG. For data collected during mimicked static positions, averages of 50 stimuli were taken.

EMG analysis

EMG activity during movement

To provide an indicator of the level of activity occurring in the arm muscles during walking, analysis of control EMG amplitudes was conducted across all 16 bins of the movement cycle. To quantify background EMG patterns during walking, a modulation index ($MI = [(EMG_{max} - EMG_{min}) / EMG_{max}] * 100$) was calculated for each muscle throughout the movement cycle at each of the 16 bins as used previously for arm cycling movement (Zehr & Chua, 2000; Zehr & Kido, 2001). A large MI indicates a very rhythmically active muscle and a small MI a less rhythmically active one.

Cutaneous reflexes

Reflexes were examined at early (~50-80 ms) and middle (~80-120 ms) latencies. During analysis for a given subject all subtracted reflex traces for a muscle (i.e. for all 16 bins) were superimposed and a mean and standard deviation of the prestimulus EMG was calculated as an index of subtraction error. Reflex amplitudes were considered significant and included in the analysis if they exceeded a 3 standard deviation band calculated from this prestimulus subtracted residual. To quantify reflex amplitudes, a 10 ms window centred about the maxima or minima of each response was calculated for each latency.

Statistics

Analysis of variance was used to determine main effects and stastically significant reflex amplitudes as well as phase-dependency during walking. This analysis was conducted on datasets averaged across all subjects. Tukey's HSD test was used to post-hoc significant main effects (e.g. significant differences between control and reflex EMG). Linear regression analysis was used to determine the significance of any relationships between reflex amplitude and background EMG during standing and walking. For this analysis all data from standing and walking for each subject were used. Descriptive statistics included means ± standard error of the mean (SEM). Statistical significance was set at $p < 0.05$.

Results

Phase-modulation of cutaneous reflexes during walking

Examples of reflexes evoked in all 8 arm muscles are plotted for a single subject in Figure 1. Averaged sweeps from each of the 16 bins have been superimposed for each muscle. Note the prominent reflexes in all muscles on the ipsilateral side and smaller but still obvious responses in contralateral AD, PD, and TB. Indicated in Figure 2 are the amplitudes of reflex responses at early and middle latencies for all 8 muscles studied and averaged across all subjects. As shown, reflex amplitudes were typically modulated by position in the walking cycle. Significant early latency responses were seen in iPD, iBB, iTB, and cTB. Responses at early latency tended to be excitatory on the ipsilateral side but could be either inhibitory or excitatory on the contralateral side (e.g. contrast bin 2 excitation in iTB with inhibition in cTB). Middle latency reflex amplitudes were significant across the group of subjects for iPD, cPD and iTB.

Task-dependency of cutaneous reflexes

To determine task-dependency, cutaneous reflex amplitudes were plotted as a function of background EMG for the 5 static postures and for the 16 bins of the step cycle. Significant correlation was seen between EMG level and cutaneous reflex amplitude only during static contraction (see Table 1). As can be seen in Table 1, for both early (6 of 8 muscles) and middle latency (6 of 8 muscles) reflexes a significant slope was observed between reflex amplitude and background EMG while holding the static positions. In contrast, no significant

Figure 1

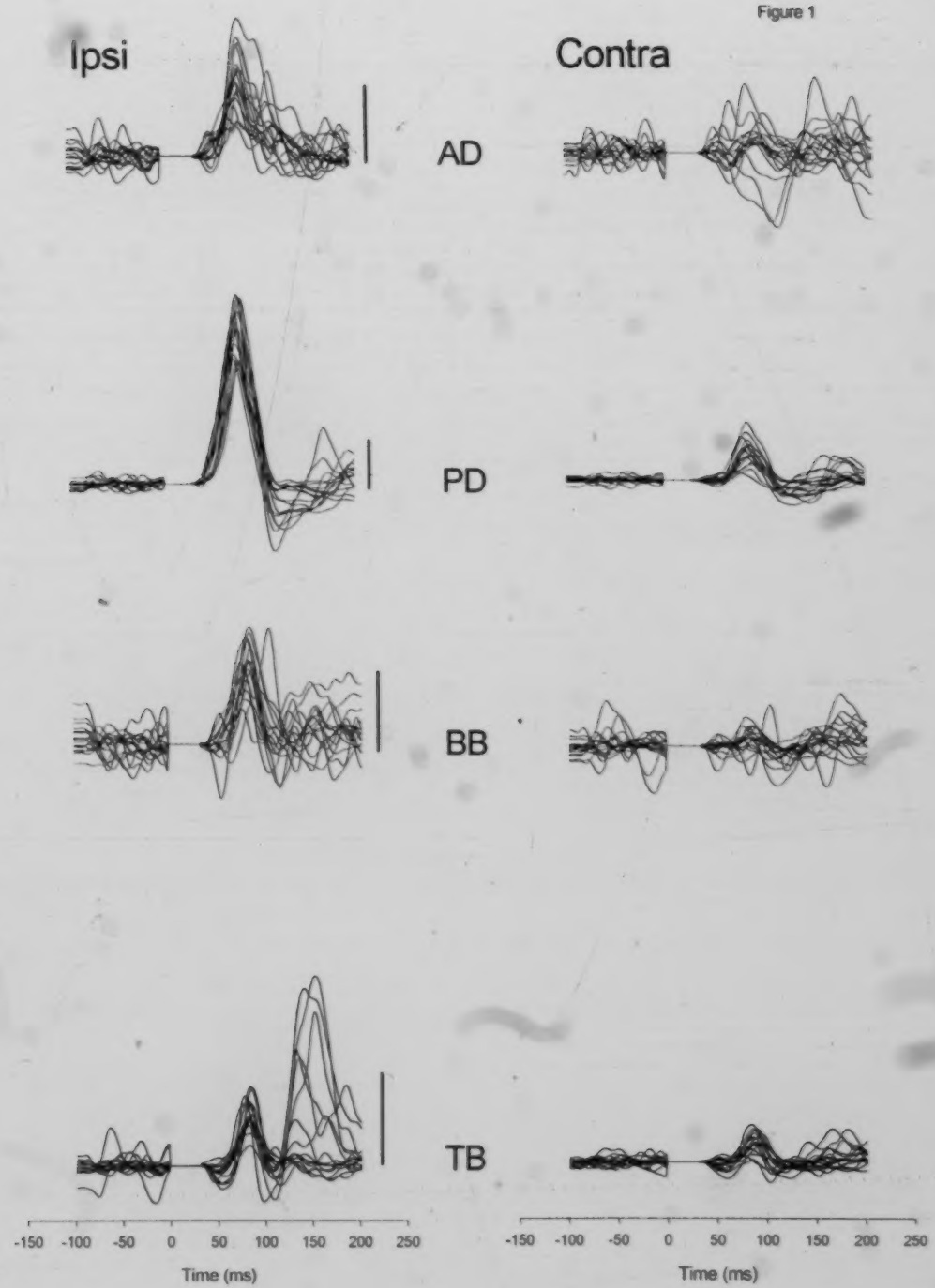
Ipsi
Contra
AD
PD
BB
TB
-150 -100 -50 0 50 100 150 200 250
Time (ms)
-150 -100 -50 0 50 100 150 200 250
Time (ms)

Figure 2

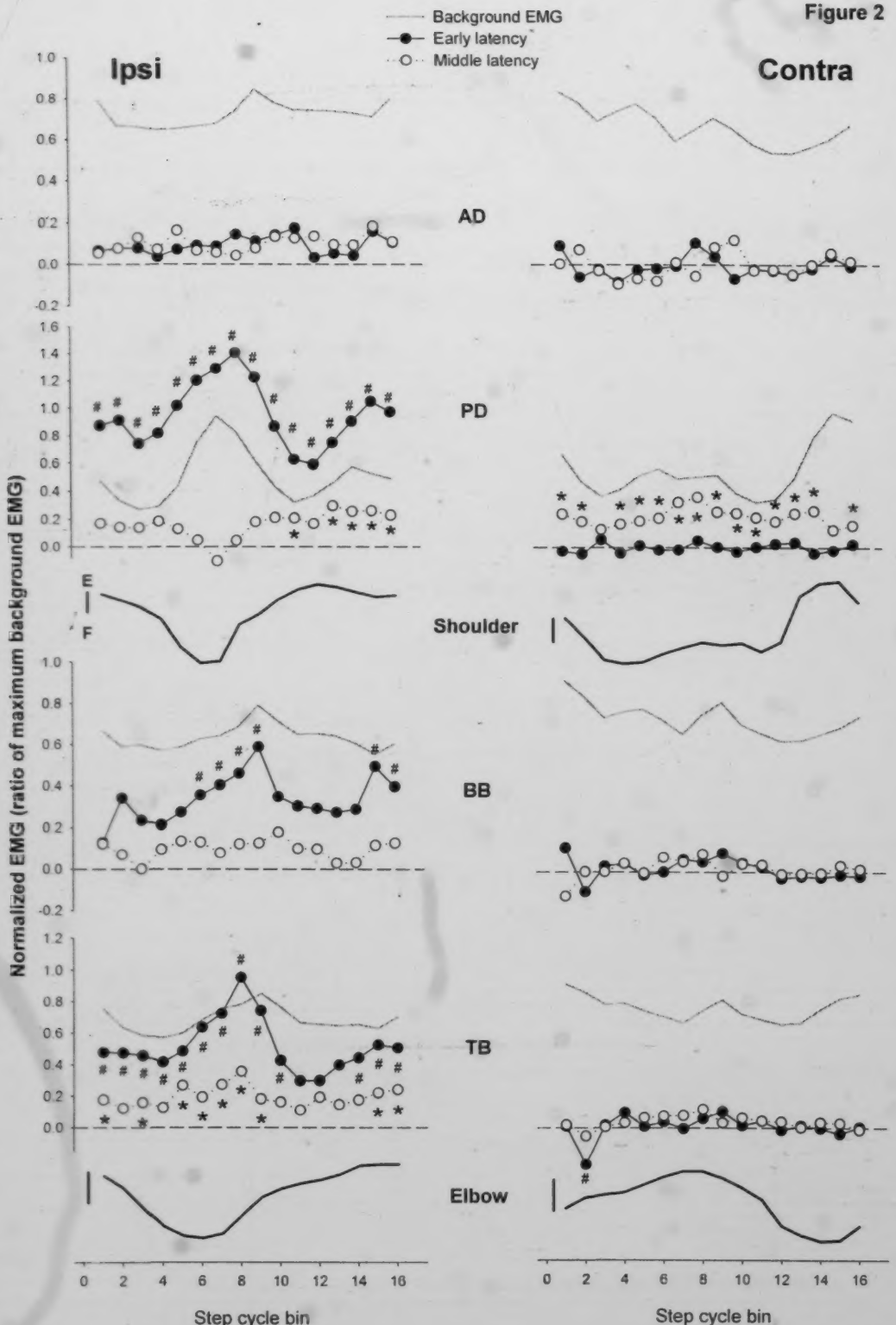
Background EMG
Early latency
Middle latency
Ipsi
Contra
AD
PD
E
F
Shoulder
BB
TB
Elbow
Normalized EMG (ratio of maximum background EMG)
Step cycle bin
Step cycle bin

Table 1: Summary of linear regression analysis between early and middle latency SR nerve reflexes and background EMG during standing and walking. Significant Pearson correlation coefficients (r) are indicated by asterisks (* $p < 0.05$, ** $p < 0.01$, NS not significant). Abbreviations as in Figure 1.

Muscle	Task	Pearson r value early	Pearson r value middle			Pearson r value early	Pearson r value middle
iAD	Static	-0.67**	0.87**	cAD	static	-0.95**	0.79**
	Walking	NS	NS		walking	NS	NS
iPD	Static	NS	-0.54*	cPD	static	-0.63**	NS
	Walking	NS	NS		walking	NS	NS
iBB	Static	-0.53*	0.57*	cBB	static	-0.54*	0.73**
	Walking	NS	NS		walking	NS	NS
iTB	Static	NS	NS	cTB	static	-0.73**	0.81**
	Walking	NS	NS		walking	NS	NS

relationships were observed during walking. However, it must be noted that EMG levels in many muscles were much higher during static contraction compared to walking (not shown). To evaluate the effect that different ranges of EMG levels might have had on the regression analysis, we also examined the static data over truncated ranges that were more comparable to the levels seen during walking. Despite the large reduction in data points due to this analysis, significant correlations were still observed when regression performed on the static data evaluated over these truncated ranges. However, the number of significant correlations dropped to 63% for early and 38% for middle latency responses. Additionally, the modulation of early and middle latency reflex amplitudes due to changes in static postures was also examined. For iAD, iPD, iBB, and cAD main effects for posture were observed suggesting modulation of reflex amplitudes during static contraction. However in all these cases, modulation of reflex amplitude occurred along with changes in EMG levels.

EMG patterns of arm muscles and kinematics during walking

As shown in Figure 2 (solid gray lines in each panel), rhythmic patterns of activation between flexors and extensors within a limb and between homologous muscles across the body were observed. Flexors BB and AD were often coactive and antagonistic muscles AD and PD were out of phase with each other. There was a shallow modulation of AD whereas PD activity was deeply modulated bilaterally. Interestingly, there was cocontraction between BB and TB. The modulation indices for AD were 43.7% and 50.3%, PD 75.3% and 72.5%, BB

54.2% and 41%, and TB 49.9% and 37.8% for the ipsilateral and contralateral sides, respectively.

In Figure 2 average kinematic data from shoulder (middle of figure) and elbow (bottom of figure) joints are shown as solid black lines. Extension at the shoulder (shown as an upward deflection indicated by "E" on the calibration bars) can be seen to parallel PD activity.

Discussion

Two new observations revealed by this work are that: 1) amplitudes of cutaneous reflexes in upper limb muscles are phase-modulated throughout the walking cycle; and 2) there is significant task-dependent modulation of cutaneous reflexes in arm muscles when comparing walking to static postural contraction. This is the first attempt to study cutaneous reflexes in arm muscles evoked by stimulation of nerves innervating the hand during walking. These observations agree with our previous results on phase and task-modulation of cutaneous reflexes during arm cycling (Zehr & Chua, 2000; Zehr & Kido, 2001).

Arm muscle EMG patterns while walking

While still displaying a rhythmic pattern, EMG activity in AD and BB showed a different pattern of modulation from that documented during arm cycling (Zehr & Chua, 2000; Zehr & Kido, 2001). During arm cycling, MI values for the flexors AD and BB were around ~76% and 83%, whereas here the values were ~44% and 54% respectively. In contrast, the rhythmic EMG patterns in the

extensors PD and TB were similar to that observed during arm cycling. Overall, it appears that the EMG patterns of arm muscle activity during walking are phasically modulated and are similar to those seen in the arms and legs during cycling and walking.

Comparison of reflex modulation in arm muscles during walking to observations in the leg and to arm cycling

Early latency reflexes in iAD, iBB, and iTB (see Figure 2) were phase-modulated but always excitatory, in contrast to the pattern observed during arm cycling in which early latency reflexes in these muscles were typically inhibitory (Zehr & Chua, 2000; Zehr & Kido, 2001). Early latency reflexes in iPD, cPD, and cAD were modulated similarly to that seen during arm cycling, while for cTB and cBB there are no comparable data available. This suggests very similar control mechanisms for rhythmic, cyclical arm movements. Interestingly, early latency reflexes in arm muscles are consistently present both here during walking and in arm cycling (Zehr & Chua, 2000; Zehr & Kido, 2001). This is of note because early latency responses are typical inconsistently found in leg muscles during walking (Duysens et al., 1992; Van Wezel et al., 1997). At middle latency, the pattern of modulation (phase-modulated but typically excitatory) for all 8 muscles was quite similar to that seen after SR nerve stimulation during arm cycling (Zehr & Kido, 2001). This further suggests a similar control mechanism for middle latency reflexes during both arm cycling and walking.

A role for CPG mechanisms in the neural control of arm muscle activity during walking

As mentioned in the Introduction, the modulation pattern of cutaneous reflexes during movement can provide insight into the mechanisms controlling the movement itself. Another way to examine the phase- and task-modulation of cutaneous reflexes is to plot the reflex amplitude as a function of the EMG level at the time the reflexes are sampled. This analysis will reveal if the reflex amplitude simply scales with background EMG level (in which case there will be significant linear relationship; e.g. gain compensation (Matthews, 1986)) or if there is independence between background EMG and reflex amplitudes (in which case no significant correlation will be observed). Lack of correlation between reflex amplitude and EMG level has been ascribed to the activity of CPG networks gating reflex transmission to the legs during walking (Komiyama et al., 2000; Van Wezel et al., 1997) and leg cycling (Zehr et al., 2001), and to the arms during cycling (Zehr & Kido, 2001). In the present study, reflexes in most muscles were phase-modulated (see Figure 2). Importantly, the majority of muscles (12 of 16 possible combinations for both latencies) also showed significant linear relationships between early and middle latency reflex amplitudes and EMG levels during static contraction (see Table 1). Furthermore, in those instances where reflex amplitude was modulated by changes in the static postures, this modulation was entirely explained by changes in EMG level. In contrast, during walking significant correlation between reflex amplitude and EMG level was absent. When comparing reflex amplitudes during standing to those during

walking and running, cutaneous reflexes are significantly task-modulated (Duysens et al., 1993; Komiyama et al., 2000). Following the logic advanced for leg muscle reflexes, a similar observation here in arm muscles during walking suggests activity of CPG networks. It might be suggested that simple changes in postural orientation or EMG synergies might underlie the patterns of reflex modulation. However, position alone does not significantly modulate cutaneous reflexes during walking (Duysens et al., 1993), arm cycling (Zehr & Kido, 2001) or leg cycling (Brooke et al., 1999; Brown & Kukulka, 1993). This was also clearly shown in the recent work of Dietz et al. (2001), wherein reflexes in arm muscles evoked by stimulation at the ankle were only present during the performance of locomotor tasks (Wannier et al., 2001). Taken together, our work further corroborates the assertion that the rhythmic arm movement seen during human walking and arm cycling may be controlled by CPG circuits at least partially resident in the spinal cord (Dietz, 2002; Jackson, 1983). It must be stated, however, that this is indirect and inferential evidence. Additionally, the transit time for the middle latency reflexes are certainly long enough to allow for supraspinal contributions (Christensen et al., 2000) to the responses and thus a supraspinal contribution cannot be excluded.

In conclusion, cutaneous reflexes in arm muscles are task- and phase-modulated during walking. The results from this study further add to the accumulating evidence that rhythmic arm and leg movements share similar neural control mechanisms. These results support the assertion that rhythmic arm movement during walking may be controlled, at least in part, by spinal

central pattern generators. This extends observations from earlier research focused upon arm cycling movement, and thus provides further support for a broadly applicable neural control strategy for rhythmic movement in humans.

Figure legends

Figure 1. Subtracted EMG traces from a single subject showing reflexes evoked by SR nerve stimulation obtained during walking. Reflex traces for each of the 16 parts of the step cycle have been superimposed in each panel. Stimulus artifact has been removed from 0 to ~30 ms post-stimulus and is shown as a flat horizontal line during this period. Muscle abbreviations are AD (anterior deltoid), PD (posterior deltoid), BB (biceps brachii), TB (triceps brachii), Ipsi (ipsilateral to stimulation), Contra (contralateral to stimulation). Calibration bars are 1, 5, 2, and 5 μV, for AD, PD, BB, and TB, respectively. Ipsi and Contra muscles are plotted on the same scales.

Figure 2. Phase-modulation of cutaneous reflexes in arm muscles observed throughout the walking cycle. Shown in each panel are subtracted reflex amplitudes at early (<80 ms; filled circles) and middle latency (80-120 ms; open circles). Additionally, the control (unstimulated) EMG amplitudes for each muscle are indicated by the thick gray lines at the top of each panel. Values are means across all subjects. Bin 1 represents right heel contact. Error bars have been omitted for clarity. Kinematic recordings from shoulder and elbow joints are drawn as black lines. The calibration bars indicate 5° for shoulder and 10° for elbow movement. Abbreviations are as in Figure 1. E (extension direction), F (flexion direction). #,* $p<0.05$ for early and middle latency responses, respectively.

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